Emergency Management in Neurology
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Hemorrhagic Stroke

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Emergency Management in Neurology

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Presentation of the Series

Emergency in Neurology: A Practical Approach is a series of books which deal with the most significant chapters in the scenario of neurological emergencies, in terms of diagnosis, differential diagnosis and therapy. One particularity of the philosophy of all the books is the close integration between the strictly clinical-scientific aspects and the organizational elements, which are so important for the efficiency and effectiveness of the treatment.

The main themes of the individual volumes are as follows:

- Ischemic stroke
- Hemorrhagic stroke
- Neurological emergency during pregnancy
- Neurological emergency in paediatrics
- Acute loss of consciousness
- Emergencies in neuromuscular disease
- Delirium, stupor and coma
- Neurological infections
- Spinal emergencies
- Cerebral hyper/hypotension syndrome
- Diagnostic tools in neurological emergencies
- Emergency medical network in neurological disease

All the volumes are structured in the same way, each containing the following chapters:

A. The first chapter is an overview of the most recent progress in diagnosis and therapy, including the clinical, instrumental and therapeutic aspects of the acute pathology under discussion, focusing specifically on the best clinical practices.

B. A chapter dedicated to clinical pathways and the associated organizational elements, following principles which inspired the international guidelines.
C. A review of clinical cases that are typical of the diverse clinical situations presented daily to the doctors involved in managing neurological emergencies. After the presentation of each clinical case, the reader finds a series of questions and topics regarding the case's management and some observations by the co-ordinator of the series.
D. A section dedicated to the differentiated algorithms used for decision-making, based on the organizational, structural and technological features of the hospital receiving the clinical case. This final section of each book is extremely important for the day-to-day handling of neurological emergencies. This chapter aims to supply the reader with all the elements necessary to apply the guidelines and send the patient on the best clinical pathway, taking into consideration the diagnostic and therapeutic opportunities available.

The aim of this series is to provide the specialist with a useful tool for improving the outcome for patients with acute and/or time-dependent neurological pathologies, by choosing a dedicated clinical pathway according to the best practices and scenarios of the professional and organizational opportunities offered by the clinical centres.

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Preface

The acute phase of hemorrhagic stroke is a neurological emergency. Management of an acute hemorrhagic stroke requires a complex series of programmes and timely actions which can assure that the process is efficient and the treatment effective. The context of cerebral hemorrhage is complicated by the presence of various clinical-pathological entities, represented by primary and secondary intraparenchymal hemorrhage and by subarachnoid hemorrhage, with its numerous causes. A new role is emerging in this scenario: that of a multidisciplinary team which works closely together and is able to make the correct diagnostic and therapeutic choices, taking into consideration the hospital's organizational set-up. This scenario makes it ever more necessary to have a dedicated organization whose aim is to guarantee, always and everywhere, the best treatment for patients with hemorrhagic stroke.

This volume aims to provide the specialist with a reference tool which will help him to send the hemorrhagic stroke patient along the pathway in the most efficient and coherent manner, taking directions from scientific literature and international guidelines. The scope of stroke management is extremely complex, and its developments are a fundamental point of reference for directing diagnostic, clinical and instrumental choices, for selecting the patients who qualify for the best therapy and for defining the aspects of their prognosis. This book applies a dynamic methodology to deal with current diagnostic aspects and the latest directions in the guidelines. Real clinical cases are introduced which record the various stages of the problems, the diagnostic-therapeutic

decisions and the patients' clinical pathways: the decision to include these cases derived from observing the daily reality, which is then presented to the reader in a critical way through the reflections and comments of clinical experts.

The importance of this book lies in its determination to put best clinical practice into real-life contexts, without losing sight of the organizational characteristics of the hospitals receiving the hemorrhagic stroke patient. In keeping with this concept, the diagnostic-therapeutic pathways for hemorrhagic stroke are differentiated according to the technical, professional and structural characteristics of the hospitals and by identifying the various organizational settings, which are the guiding principle of differentiated clinical pathways. The layout of this volume places the reader in a real situation and offers the clinical expert the chance to choose the best pathway, also taking into consideration the functional features of the hospital where the case is handled. This paradigm facilitates the development of pathological networks and broadens the concept of the 'hub and spoke' organization for accurately managing acute hemorrhagic stroke. In this scenario, the structural and organizational characteristics of the clinical centres are used to differentiate the clinical pathways for patients with hemorrhagic stroke, thus facilitating the clinical expert in his choices and highlighting the importance of operative cooperation between the centres in the network.

Milan, Italy The Series Editor and the Authors

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Abbreviations

AEDs	Anti-Epileptic Drugs
AHA	American Heart Association
ASA	American Stroke Association
aPTT	activated partial thromboplastin time
AVM	Arteriovenous malformation
BP	Blood Pressure
CAA	Cerebral amyloid angiopathy
CCB	Calcium channel blocker
CHL	Cerebral hemorrhagic lesion
CSF	Cerebrospinal Fluid
CPR	Cardiopulmonary resuscitation
CPSS	Cincinnati Prehospital Stroke Scale
CT	Computed tomography
CTA	Computed tomography angiography
DAF	Dural arteriovenous fistula
DALYs	Disability-adjusted life years
DCI	Delayed cerebral ischemia
DSA	Digital subtraction angiography
DVT	Deep vein thrombosis
DWI	Diffusione Weighted Imaging
EBI	Early brain injury
ECG	Electrocardiogram
EEG	Electro Encephalo Gram
ESO	European Stroke Organization
EVD	External ventricular drain
ER	Emergency room
EVS	External ventricular shunt
FFP	Fresh frozen plasma
FLAIR	Fluid-attenuated inversion recovery

GCS	Glasgow Coma Scale
GCP	Good clinical practice
HF	Heart failure
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
ICU	Intensive care unit
ISAT	International subarachnoid aneurysm trial
INR	International Normalized Ratio
IV	Intra venous
IVH	Intraventricular hemorrhage
LMWH	Low-molecular-weight heparin
MCA	Middle cerebral artery
MRA	Magnetic Resonance Angiography
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NIHSS	National Institutes of Health Stroke Scale
NE	Neurological examination
OAT	Oral anticoagulation therapy
PAASH	Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage
PCC	Prothrombin complex concentrate
PICA	Posterior inferior cerebellar artery
PTA	Percutaneous transluminal angioplasty
rtPA	recombinant tissue Plasminogen Activator
SAH	Subarachnoid hemorrhage
SBP	Systolic Blood Pressure
SD	Spreading depolarization
SIRS	Systemic inflammatory response syndrome
SPREAD	Stroke Prevention an Educational Awareness Diffusion
SWI	Susceptibility weighted imaging
TCD	Transcranial Doppler
WFNS	World Federation of Neurological Surgeons

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Chapter 1
Diagnosis and Therapy in the Acute Phase of Hemorrhagic Stroke: Latest Developments

Edoardo Boccardi, Marco Cenzato, Francesco Curto, and Cristina Motto

Hemorrhagic stroke includes spontaneous intracerebral hemorrhage and subarachnoid hemorrhage, and although they represent, respectively, about 15 and 5 % of all strokes, they are an important public health problem throughout the world, due to the elevated rates of mortality and disability, which are higher than in ischemic stroke.

In addition, the global impact of hemorrhagic stroke has significantly increased in recent decades: between 1990 and 2010, there was an increase of 47 % in terms of the absolute number of people affected by the disease. This is mainly due to a significant increase in incidence in low- and middle-income countries (+22 %; 95 % CI 5–30 %), while in high-income countries the incidence has significantly decreased (–19 %; 95 % CI 1–15 %) [1].

According to the same report [1], the prognosis has improved in both high-income and low- and middle-income countries, although in different proportions: reduction in mortality of 38 and 23 %, reduction of Disability-Adjusted Life Years (DALYs) lost 39 and 25 %, and reduction in mortality-to-incidence ratios 27 and 36 %, respectively, probably due to improved disease management.

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Hemorrhagic stroke is a medical emergency and must be diagnosed and managed in a timely manner because of the high risk of clinical deterioration in the first hours after the onset of symptoms. Since intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) recognize different aetiologies and treatments, they will be treated separately.

1.1 Intraparenchymal Brain Hemorrhage

ICH is a focal parenchymal cerebral bleed caused by the rupture of a vessel, resulting in compression and disruption of the brain tissue. It can spread to other cerebral compartments, such as ventricles, rarely the subdural or subarachnoid space.

1.1.1 Epidemiology

The annual incidence of ICH is 24.6 cases per 100,000 inhabitants (95 % CI 19.7–30.7) [2], gradually increasing with age [2–4]. It accounts for 10–15 % of all brain strokes [5], with a variability relating to geographic areas and age. ICH is prevalent in the Asian population where it accounts for 30 % of all strokes [6] and in the age group under 45 years, in which ICH and SAH are 25–55 % of the total number of strokes [7].

ICH occurs more frequently in men than in women in all age groups [2, 8], especially in Japanese population [2]. As for ethnicity, there is a higher prevalence of ICH in Asian [2, 5] and black populations [9] which might be correlated to the higher prevalence of hypertension.

1.1.2 Aetiology

ICH can have primary and secondary causes.

Among the primary causes are hypertensive angiopathy and cerebral amyloid angiopathy (CAA).

Hypertensive Angiopathy

High blood pressure is the most important cause of ICH [10] and 50 % of all ICH is caused by hypertension. Hypertensive angiopathy is the predominant cause of ICH also in subjects aged between 40 and 50 years [11]. High blood pressure increases the risk of ICH particularly in patients who do not comply to hypertension therapy and in patients younger than 55 years old who are habitual smokers [12].

By contrast, appropriate control of arterial hypertension reduces the risk of ICH. The majority of ICH related to hypertensive angiopathy occurs because of the rupturing of small perforating arteries such as lenticulostriate, thalamus perforating arteries and the arteries that originate from the basilar artery.

Cerebral Amyloid Angiopathy (CAA)

CAA accounts for 5–20 % of the causes of ICH [13, 14] and is typical of the elderly. Amyloid angiopathy is characterized by the progressive deposit of amyloid-beta peptides in the small and medium-diameter capillaries, arterioles and arteries of the cerebral cortex, leptomeninges and cerebellum, causing degenerative alterations that reduce the compliance of the vessel and cause micro-hemorrhages or symptomatic ICH [13, 15].

The location of ICH related to this disease is typically lobar and less frequently cerebellar, rarely deep, and reflects the distribution of pathological changes of microangiopathy. It is a disease that affects the elderly population and is commonly associated with changes in the gene coding for apolipoprotein E [5]. The juvenile familial form is typically associated with mutations in the gene coding for the amyloid precursor protein [16].

Leukoaraiosis and micro-cortical infarcts are associated with CAA and are probably caused by a chronic hypoperfusion of the arteries affected by amyloid angiopathy [13, 17].

Secondary causes of ICH are as follows:

- Vascular malformations: arteriovenous malformations (AVMs), dural arteriovenous fistulas DAVFs, aneurysms, cavernous angiomas, venous angiomas, Moyamoya syndrome and telangiectasias
- Coagulopathies: secondary to taking anticoagulants, antiplatelets and thrombolytics and congenital and acquired hemorrhagic diathesis (deficiency of coagulation factors, quantitative or qualitative platelet abnormalities)
- Exogenous substances (cocaine, amphetamines, alcohol)
- Brain tumours and metastases (melanoma, lung cancer, renal cell carcinoma, testicular carcinoma, choriocarcinoma)
- Cerebral venous thrombosis
- Infectious and inflammatory diseases (septic arteritis, mycotic aneurysms, hemorrhagic encephalitis of Weston-Hurst, vasculitis)

In the elderly, the most frequent causes of ICH are hypertensive angiopathy and amyloid angiopathy, ICH associated with anticoagulant drugs and cancer, while in young people the most frequent causes are vascular malformations, substance abuse and coagulopathy.

Location

ICH frequently occurs in the cerebral lobes, basal ganglia, thalamus, brainstem – mostly pons – and cerebellum. Therefore, the locations are defined as lobar, deep, and infratentorial. The deep location is the most frequent and represents about 45 % of all ICH; the lobar location accounts for 30–40 % of all ICH, the cerebellar location 10 % and the brainstem location about 5 %. There may however be differences depending on the characteristics of the study population.

The breakdown by location is reflected in the recognition of different processes of aetiology [18], while the 1-year survivals of ICH in lobar and deep locations are substantially comparable: 45.4 %–59.1 % and 45.4 %–59.4 %, respectively [19]. Deep and vast ICH can extend into the ventricles.

1.1.3 Prognosis

ICH is the type of stroke which leads to higher mortality and disability. 30-day mortality is estimated at between 32 and 50 % [2, 4, 20] and the 1-year survival is 46 % [19]; only 28–35 % of the patients who survive are independent 3 months after the acute event. In ICH patients, the "do not resuscitate" order is quite frequent and reaches 35 % in a recent study [21]. Factors associated with the "do not resuscitate" order are advanced age, ICH severity and early clinical deterioration.

Neurological deterioration commonly occurs in the first hours after onset of symptoms: 20 % of patients present it in the pre-hospital phase; a further 15–23 % of patients show signs of clinical deterioration after arriving at the hospital [22]. Neurological deterioration often signals constant bleeding resulting in expansion of the hematoma.

Prognostic Factors

Some of the factors that negatively affect the prognosis have been identified: age, state of consciousness, blood pressure, diabetes, elevated blood glucose on admission, hematoma volume, endoventricular extension of the hemorrhage, perihemorragic oedema, hydrocephalus, concomitant anticoagulant therapy, increased troponin and hyperpyrexia.

Hematoma expansion, intraventricular extension of the hemorrhage with hydrocephalus, hyperglycaemia and perihemorragic oedema are the major predictors of poor outcome in the acute phase of ICH [23].

Hematoma Volume

Among the prognostic factors, the volume of the hematoma is the most significant as it is associated with an increased risk of mortality [24, 25]. A haematoma volume exceeding 50 ml is associated with an unfavourable prognosis. In the first hours after the onset of symptoms, the haematoma can expand as a result of continuous bleeding.

Haematomas generally expand during the first 3 h after onset of symptoms, although a volumetric expansion is possible until 12 h [5]. Increases of various degrees in the volume of hematomas have been observed in up to 73 % of patients evaluated within 3 h of onset of symptoms [26–28]. In more than 35 % of patients struck by ICH, hematomas expanded by more than a third of the initial volume [26].

An algorithm called BRAIN has been proposed and validated in order to predict the risk of ICH growth. This algorithm is scored on 24 points deriving from the INTERACT2 study and based on the volume of the hematoma on the basal patient's brain CT scan (score per ml of volume <10 = 0, 10–20 = 5>7 = 20), recurrent ICH (yes = 4), anticoagulant therapy with warfarin on onset of symptoms (yes = 6), endoventricular extension (yes = 2) and number of hours from onset of symptoms to brain CT scan (<1 = 5, 1–2 = 4, 2–3 = 3, 3–4 = 2, 4–5 = 1, >5 = 0).

The probability of the hematoma growing varies from 3.4 % for 0 points to 85.8 % for 24 points [29]. This scale is intended to stratify the risk of hematoma growth for clinical and research purposes.

Intraventricular Bleeding in ICH

ICH in the ventricles expands in up to 30–50 % of cases and can be observed in both the early and late phases of the disease [23]. The presence of intraventricular hemorrhage (IVH) bleeding is associated with an unfavourable prognosis [24] and the amount of blood in the ventricles directly correlates with the extent of damage and the probability of survival.

In the INTERACT 2 study, a strong association was observed between the amount of endoventricular bleeding

and an unfavourable prognosis, with a cut-off volume of 5–10 ml, above which mortality and disability 90 days after the major event increase significantly [30].

Observational studies have shown that endoventricular administration of thrombolytic facilitates the resolution of intraventricular hemorrhage with or without ICH, reduces intracranial pressure (ICP) and duration of the external ventricular shunt (EVS), and could improve the prognosis for patients.

A clinical randomized and controlled double-blind CLEAR III study (Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage) is currently being carried out in order to assess the effectiveness of the therapy. This study includes patients with IVH, with or without supratentorial ICH with a volume of <30 ml and no underlying vascular abnormalities or coagulopathies, and who require the positioning of EVS. They are randomized to rtPA or placebo [31].

Peri-hemorrhagic Oedema

Oedema develops around the ICH and grows in the first 24 h, peaking around the 5th–6th day and lasting about 14 days [5, 32]. It is an independent negative prognostic factor and adversely affects the prognosis [33].

Statins

The association between statins and ICH is controversial. A recent meta-analysis suggests that the use of statins before a spontaneous ICH increases neither short-term mortality nor disability [34].

1.1.4 Diagnosis

ICH is a medical emergency and rapid diagnosis of the aetiology of the bleeding is also essential for appropriate management of the patient.

Clinical Presentation

ICH presents with acute onset of focal neurologic deficits often accompanied by headache, vomiting and/or alteration of conscious, depending on the location and size of the ICH. Altered consciousness occurs frequently and in a large-scale study only 28 % of patients with ICH had a normal level of consciousness; 30 % of patients were in a coma [35]. The progression of symptoms is observed in 51–63 % of patients, in higher proportions than in ischemic stroke (5–20 %), and it signals an enlargement of the ICH caused by persistent bleeding.

The most frequent clinical features of ICH, such as the onset of headache, impaired consciousness and vomiting, have been used to build diagnostic scales that help distinguish clinically hemorrhagic stroke from ischemic stroke. However, validation studies have not demonstrated a high reliability of ICH diagnosis and clinical data alone is not sufficient to clearly differentiate ischemic from hemorrhagic stroke. The use of neuroimaging is mandatory, given the imperative need to differentiate between the two types of stroke in order to establish the most appropriate treatment.

The clinical severity of the ICH can be assessed using the National Institute Health Stroke Scale (NIHSS), a standardized and reproducible rating scale that retraces the neurological examination and which is commonly used in ischemic stroke. However, the altered consciousness that commonly occurs in ICH means that this scale is not always applicable; in these cases the Glasgow Coma Scale (GCS) is used.

The initial GCS score and the volume of ICH are the best predictors of mortality rate at 1 month from the event [20].

Several prognostic scales have been proposed over time; the most used is the ICH score that takes into account factors that have proven to have a prognostic role: GCS, hematoma volume, presence of endoventricular blood, hematoma location and age (see Appendix) [36]. It is a 5-item scale with a range from 0 (excellent prognosis) to 6 (high probability of death) and with a good degree of correlation with mortality after 30 days and functional prognosis after 1 year [37].

Instrumental Diagnosis

Although the sudden onset of symptoms with headache, vomiting, impaired consciousness and rapid deterioration of vigilance may suggest the diagnosis of ICH, the definitive diagnosis is given by computed tomography (CT). The ICH appears on CT as a hyperdense lesion from the outset. The CT scan allows adequate assessment of the location and size of the hematoma and the presence of peri-hematoma oedema and intraventricular bleeding. The examination is rapidly performed and communicated to the emergency departments, allowing an immediate distinction between ischemic stroke and hemorrhagic stroke, thus leading to the most appropriate treatment being delivered in the hyperacute phase.

Magnetic resonance imaging (MRI) with gradient echo sequences can detect hyperacute intracranial hemorrhage with a degree of sensitivity and accuracy that is comparable to CT [38, 39], but this examination is difficult to use in emergency due to the time required, the need for the patient's cooperation, its poor distribution in emergency areas, as well as its cost.

MRI with susceptibility weighted imaging (SWI), particularly sensitive in highlighting haemoglobin degradation products, is more sensitive than CT scans for detecting microbleeding and previous hemorrhages, as well as detecting structural alterations such as vascular malformations and tumours; it is the preferred choice for diagnosing cavernomas [40].

If an MRI shows findings such as lobar microbleeds, superficial siderosis and white matter hyperintensity, this leads towards the diagnosis of amyloid angiopathy. Therefore, it is a valuable tool for the aetiologic diagnosis of ICH, especially if performed after re-absorption of the hemorrhage.

The multilayer CT angiography (CTA) and CT venography can identify vascular anomalies at the base of ICH, e.g. MAV, aneurysms and venous thromboses. A meta-analysis showed that the diagnostic accuracy of CTA compared to

digital angiography (DSA) in ICH is 98.2 %, with a positive predictive value of 97.8 % and negative predictive value of 98.5 %, sensitivity 97.0 % and specificity 98.9 %; the false negative rate was 1 % [41]. The CTA might therefore replace DSA in the initial vascular aetiological diagnosis of ICH in the acute phase.

The contrast-enhanced CT and CTA can highlight the possible presence of a "spot sign", which was described in 1999 and is defined as a small extravasation of contrast in one or more points of the hematoma. The "spot sign" is visible in about a third of patients with ICH and implies continuous bleeding from the broken vessel. Many single-centre studies have identified the spot sign as a predictor of haematoma expansion in patients undergoing CT within the first few hours of onset of symptoms.

The results were confirmed by the multi-centre observational study PREDICT [42] in which the "spot sign" was observed in 27 % of the 228 patients included in the study and was associated with an increased volume of hematoma and with a deterioration of the patients' neurological condition. Although the "spot sign" may be a biomarker of enlargement of the hematoma, it should be used with caution.

Cerebral angiography remains the "gold standard" examination for detecting vascular malformations and vasculitis in patients with ICH and should be contemplated in all cases without an obvious cause of ICH and in which previous clinical investigations did not offer a solution. Cerebral angiography is also indicated in people under 55 years with deep ICH [43]. If the results are negative, the vascular diagnostics should be repeated 3–6 months after onset of symptoms.

Blood Tests

Blood tests rarely identify the cause of the ICH but can provide indirect information that may contribute to the diagnosis (e.g. inflammatory markers in vasculitis, coagulation abnormalities, abnormal liver enzymes in alcoholics). Blood tests should be complete; on young patients a toxicological

examination should be performed to evaluate the possible use of illicit drugs (cocaine, amphetamines, ecstasy).

1.1.5 Treatment of the Acute Phase

Treatment of the acute phase includes general interventions for critically ill patients, such as airway management, and specific treatments for ICH designed to prevent expansion of the hematoma, reduce intracranial hypertension and treat and prevent complications. Treatment of high blood pressure and intracranial hypertension as well as restoration of coagulation should be carried out beforehand in the emergency departments where patients with ICH are evaluated.

The risk of neurological deterioration and cardiac instability is higher in the first 24 h after onset of symptoms; clinical and haemodynamic monitoring should be carried out in intensive/semi-intensive care units. Admission to a stroke unit results in a significant improvement in the prognosis of patients. Furthermore, the mortality rate is significantly lower in patients treated in a stroke unit compared to those treated on a medical ward (risk ratio (RR) 0.73; 95% CI 0.54–0.97, p=0.02) [44].

Medical Treatment

Blood Pressure Treatment

Elevated blood pressure (BP) values are reported in approximately 90 % of patients with ICH in the acute phase [45]. A large observational study showed that 75 % of ICH patients had systolic blood pressure >140 mmHg and 20 % of patients had >180 mmHg at onset of symptoms [46]. High blood values may be secondary to pre-existing, poorly controlled hypertension, altered autonomic regulation due to ICH and reaction to the increase in intracranial pressure, pain and neuroendocrine stress response.

Elevated blood pressure values are strongly associated with hematoma expansion, neurological deterioration and

poor prognosis, as demonstrated in observational studies [47]. The effect of a rapid lowering of blood pressure in acute ICH patients was evaluated in randomized, controlled clinical trials (ATACH and INTERACT) [48, 49], which showed that aggressive reduction of blood pressure values below 140 mmHg results in a reduced risk of hematoma expansion, in the absence of adverse events. However, the same clinical trials did not show significant differences between the two treatment groups in terms of the 3-month prognosis.

INTERACT-2, a randomized, controlled, open-label study with blind assessment of primary endpoint, included 2839 ICH patients with elevated blood pressure values (systolic BP between 150 and 220 mmHg) who were treated within 6 h of onset of symptoms. This study showed that the intensive reduction of systolic BP with a target of <140 mmHg within 1 h, with a lower limit of 130 mmHg, was effective in improving the 90-day functional prognosis of the patients who had significantly lower modified Rankin scores [50]. Therefore, in acute ICH patients elevated blood pressure values should be intensively reduced until systolic values are <140 mmHg [51].

Acute Haemostatic Treatment

In order to reduce the risk of hematoma expansion and the resulting neurological deterioration, some haemostatic drugs were tested. The recombinant activated factor VII (FVIIa) promotes haemostasis at the site of the bleed and limits the extension of the hematoma. The efficacy of treating patients with acute ICH was tested within 3 h of onset of symptoms in a pilot study, with promising results [52].

Although the phase III study (FAST trial) showed a significant reduction in the risk of hematoma expansion in the group treated with FVIIa at different doses, it did not show any benefits to the prognosis. Mortality and disability at 3 months were higher in the treatment groups (FVIIa 20 ug/kg and 80 ug/kg) compared with the placebo groups, 26 % and 29 % compared to 24 %, respectively [53]. The rate of arterial

thrombosis was higher in the group treated with FVIIa at a higher dose compared to the placebo group and the lowest FVII dose.

The lack of effectiveness in the presence of stabilized hematoma expansion would suggest the need for further treatments, including surgery, to be carried out after haemostatic treatment. The analysis of FAST study subgroups suggests potential benefits in patients under 70 years, with a hematoma volume of <60 ml, intraventricular hemorrhage volume of <5 ml and time of treatment <2.5 h from onset of symptoms [53].

Tranexamic acid is currently being tested in primary ICH in the hyperacute phase. The TICH2 study is a multicentre, randomized, controlled, double-blind trial, in which tranexamic acid is administered intravenously (loading dose of 1 g in 10 min + 1 g in 8 h) within 8 h of symptom onset and compared to placebo. The efficacy of treatment is evaluated in terms of mortality and dependency at 3 months.

Coagulation Treatment in Secondary ICH After Anticoagulation Therapy

ICH associated with oral anticoagulant therapies accounts for 12–20 % of the total number [54] and is rising in relation to the increased use of these drugs in the elderly population, who already carry an increased risk of ICH. Most of those on oral anticoagulation therapy take vitamin K antagonist medications such as warfarin, but there is a steady increase in the proportion of patients treated with the new oral anticoagulants dabigatran, rivaroxaban, and apixaban. These drugs are associated with a lower risk of ICH compared to warfarin.

ICH occurring in the course of anticoagulant therapy should be rapidly treated with substances which antagonize the drug taken: protamine sulphate for unfractionated heparin and vitamin K, fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC) if the patient is on an oral anticoagulant therapy with vitamin K antagonists.

The coagulation process should be restored rapidly and preferably within 2 h of onset of symptoms [5, 47]. Vitamin K begins to exert its effect 2 h after administration and reaches its peak after 24 h [55]. Therefore, despite being part of the recoagulation treatment, it is not sufficient for speedy correction of the international normalized ratio (INR).

PCC normalizes INR within a few minutes of administration, but it carries an increased risk (low) of thrombotic events [56]. A randomized and controlled study showed that 4-factor PCC is not less effective than FFP in speedy correction of the INR: INR <1.3 was obtained within 30 min in 62.2 % with PCC and 9.6 % with FFP, the occurrence of thrombotic events was similar (7.8 vs 6.4 %) while fluid overload was greater for FFP (12.8 vs 4.9 %) [57].

The optimal value of INR to be achieved in patients suffering an ICH associated with vitamin K antagonist therapy is not clear, and the targets considered in the various studies are between 1.3 and 1.5 [47]. The recombinant factor VII can quickly normalize INR but it does not restore all vitamin K-dependent factors, so it is not recommended.

As regards the new oral anticoagulants, no substances exist at this time that are able to antagonize the effect of the drug, but specific antidotes are under study. The half-life of these drugs is short and varies from 5 to 15 h. Some studies suggest the use of PCC for inhibitors of activated factor X, rivaroxaban and apixaban [58].

Surgical Treatment

A spontaneous cerebral hemorrhage presents two problems that require the involvement of the neurosurgeon:

1. Preventing or treating any secondary damage caused by the bleed itself, due to intracranial hypertension
2. Identifying a possible vascular origin of the bleed and treating it to prevent subsequent bleeding

The presence of blood on the CT scan in an unusual location for hypertensive hematoma (thalamus basal ganglia in elderly patients with hypertension) requires neurosurgical evaluation.

Possible surgical treatment of cerebral hematoma cannot ignore identification of the underlying disease; therefore the most important aim is to understand what has bled.

The lesions that most frequently respond well to neurosurgical treatment are the following:

Vascular Disorders in Need of Neurosurgical Expertise

- Aneurysms
- Arteriovenous malformations
- Cavernous angioma
- Dural fistulas

In addition, bleeding can be caused by both intrinsic tumours (gliomas) and extrinsic tumours (metastases more frequently starting from the kidney or prostate).

Finally, there are bleeds that are not due to macroscopic causes but to microscopic vascular lesions and which are typically treated by the neurologist (hypertensive vascular disease, lobar hematoma from amyloid angiopathy); the neurosurgeon must become involved when the size of the bleed may lead to intracranial hypertension.

The subarachnoid location of a bleed typically indicates the presence of an aneurysm, while an intraparenchymal bleed generally suggests the presence of arteriovenous malformations, cavernous angiomas or dural fistulas. However, there are many cases that do not follow this schematism: for example, there may be aneurysms whose dome is in the parenchyma, thus the bleed is substantially intraparenchymal.

The availability of CT angiography in the emergency room greatly facilitates the path towards detection of a hemorrhage: performing a CT scan and CT angiography in the same diagnostic session allows a source of bleeding to be quickly identified or excluded and speeds up the diagnostic and therapeutic pathway.

Spontaneous Intraparenchymal Hematoma

The typical spontaneous intraparenchymal hematoma that is not caused by a macroscopic vascular disease is still a therapeutic problem.

In most cases, intraparenchymal hematomas caused by hypertension expand in the hours after their clinical manifestation and there is a correlation between their extension and blood pressure. There is therefore a fine line between keeping blood pressure high enough to sustain adequate perfusion in the presence of possible intracranial hypertension, and avoiding that blood pressure becomes so high that it encourages the growth of the hematoma.

The general criteria that lead the neurosurgeon to evacuate an intracranial space-occupying process are:

- Deterioration of consciousness
- Shift of the median line exceeding 5 mm.
- Unilateral disappearance of basal cisterns

These general criteria are less reliable in the case of spontaneous intraparenchymal hematomas because extensive literature has demonstrated the usefulness of surgical treatment when the clinical condition of a patient with spontaneous deep hematoma is compromised. It is believed that the very fact of reaching deep regions in the basal nuclei via surgery causes considerable damage to the brain tissue, which is likely to exceed any advantage given by the actual evacuation. Furthermore, patients are often elderly and with multiple comorbid conditions.

A multicentre trial (STITCH I) which was concluded in 2005 did not show any difference between the advantages derived from surgery and from conservative treatment of hematomas deeper than one centimetre from the cortical surface. A second trial (STICH II) [59], which ended in 2013, seemed to suggest a modest advantage derived from the surgical evacuation of lobar hematomas, but not for deep ones. STICH trials refer to traditional surgical techniques, which are certainly invasive. Some publications have highlighted the importance of emptying the hematoma with a minimally invasive endoscopic technique or using catheters and washing with thrombolytic drugs to dissolve the clot.

A multicentre trial (MISTIE III) [60, 61] is currently being carried out: the data seems promising, although it is not at the moment conclusive.

The assessment of a neurosurgeon is therefore necessary if the patient's clinical condition deteriorates or if the CT scan shows a shift of the midline. However, the criteria are not standardized and coded clinical deterioration is still a parameter that requires clinical assessment regarding the possibility of surgical evacuation.

The situation is completely different if the CT scan shows one of the vascular diseases mentioned above, which require separate, specific treatment.

Cerebral Aneurysm

It should be remembered that an aneurysm can also present with intraparenchymal bleeding and little subarachnoid blood. For treatment, see next chapter.

Arteriovenous Malformations (AVMs)

If radiological diagnostics detect an arteriovenous malformation, bleeding can have a wide range of different causes. AVM is an extremely heterogeneous disease (AVM diameters can vary from a few millimetres to more than ten centimetres; AVMs can be superficial or deep; they can have sharp margins or be diffuse) and it is one of the most complex diseases of neurosurgical interest.

AVMs must be treated by neurosurgical and neuroradiological teams experienced in managing this disease. AVM treatment should be centralized in hospitals with large series because of the wide range of variables that guide the treatment.

After several years in which endovascular treatment was prevalent for AVMs, today surgery is the treatment of choice. Endovascular treatment is reserved for specific cases.

In general the hemorrhage caused by an AVM bleed is not as clinically severe as that caused by the rupture of an aneurysm. Furthermore, the risk of an AVM re-bleeding is lower

than that of an aneurysm. For these two reasons, the treatment of an AVM that has bled is rarely considered as an emergency, except in cases of life-threatening bleeding, which rarely have a good outcome.

Given the technical complexity involved in treating an AVM, and if the patient's clinical condition allows it, surgery is preferable after a few days, when the acute phase is over and when the brain tissue is less oedematous and less tense, making surgical treatment of the malformation technically more manageable. It is rare that patients cannot be transported to a centre where they can be given the best possible treatment.

The diagnosis must be accurate and it is essential to carry out selective angiography to detect the point of possible rupture of the malformation. When the malformation is of such a size that it might reach the ventricle, not infrequently the point of rupture may be due to an aneurysm in a small vessel afferent to the malformation of the same ventricle.

Super-selective angiography, which can only be performed in a highly specialized centre, is needed to detect the point of rupture. In the acute phase, it may be appropriate to treat the site of the rupture intravascularly (if it is detectable on selective angiography) and then secure the malformation.

Today, it is no longer considered suitable to treat AVMs intravascularly with the aim of closing the entire malformation. Since endovascular treatment of AVM can involve a high number of complications, it is no longer considered a first-line treatment.

Nowadays endovascular treatment is limited to:

- Closing a possible rupture site (aneurysm on a feeder)
- Preparing for surgical treatment

In the second case, the treatment is guided by the neurosurgeon's request to selectively close some afferences to the AVM, usually the deepest afferences which are furthest from surgical access, so that bleeding can be better controlled during surgery.

In order to ensure the safety of the patient and the success of the treatment, it is essential that the neurosurgeon and the neuroradiologist understand each other and cooperate closely when choosing the endovascular and surgical strategy, which must be defined and coordinated before starting any treatment.

Indications for surgical treatment of an arteriovenous malformation are mainly related to its size and location in relation to the eloquence of the brain area affected by AVM.

The Spetzler and Martin scale score (which is based on three parameters: size, involvement of eloquent area and characteristics of the venous drainage) expresses the surgical risk. There are other more detailed and more precise scales, but the Spetzler and Martin has established itself worldwide for its simplicity and its ability to categorize an extremely heterogeneous disease [62].

Malformations with grade scores four to five (therefore large and in eloquent areas) have an extremely high risk factor during surgery and therefore no surgical solution is considered unless the conditions are life-threatening for the patient. Therapeutic solutions for these malformations have not yet been cleared and defined.

There is general consensus that reducing the volume of the malformation through partial endovascular treatments does not represent a viable therapeutic strategy; rather it increases the risk that the malformation may bleed.

There has recently been investigation into the possibility of treating large malformations with multiple radiosurgery sessions spread over several years, splitting the malformation into various target areas. The results are still preliminary but seem to be encouraging.

In 2013, a randomized multicentre study (ARUBA) [63] investigated the treatment of "unruptured" arteriovenous malformations, as a preventive treatment for bleeding.

This study has been and still is a source of numerous controversies mainly due to the fact that it grouped the possible treatments (surgical, endovascular and radiotherapy) under the single heading of "intervention", uniting incomplete,

partial endovascular treatments or gamma knife treatments for which obliteration time is over 2 years with surgery.

Although this study was published in the prestigious magazine Lancet, its findings are extremely questionable [64–67].

Surgical treatment of AVM must be performed in a specialized centre. The technical difficulty in surgical treatment of arteriovenous malformation is mainly linked to haemostasis of the small blood vessels coming from the white matter, which nourish the malformation.

Malformations normally have some big feeders and some large venous drains which are easily identifiable, but a large number of small vessels exist all around the nidus of the malformation and they are recruited and dilated by the large blood flow from the white matter.

The disproportion between the large flow inside these vessels and their very thin walls makes closure and haemostasis of these vessels very difficult. A crucial component of any neurological damage resulting from surgical treatment of arteriovenous malformations is the need to follow these vessels into the deep white matter to be able to control haemostasis.

The development of new surgical tools like non-stitch bipolar or laser has allowed much more effective control of these vessels and has significantly reduced post-operative morbidity. The surgical strategy consists in firstly identifying, isolating and closing afferent arteries and secondly isolating the AVM nidus from all afferents coming from the white matter and finally closing, blocking off the veins and removing the malformation.

The main risk with surgery is that a residue of the AVM may remain and start bleeding again in the immediate post-operative period. For this reason it is indispensable to carry out angiographic control at the end of the operation so as to exclude the presence of any residue, and any that is found must be removed.

These are long surgical procedures demanding several hours and a lot of patience.

The endovascular option is not contemplated if the arteriovenous malformation bleeds, unless the source of the bleed is clearly identifiable (aneurysm of an afferent vessel or venous ectasia).

The outcome of treating the rupture of an arteriovenous malformation is mainly linked to the patient's neurological conditions before surgery, which were caused by the bleed.

Because of the peculiar nature of malformations in which the eloquent areas often reorganize around the lesion, most of the neurological deficits caused by bleeding and/or surgery are recovered after some time; therefore evaluation of the outcome cannot be made until 6 months after the event.

Neurological recovery is closely related to the neurological condition on presentation (GCS) and the Spetzler and Martin value of AVM. Overall, only 63 % of patients who have suffered a bleed due to an arteriovenous malformation have a good clinical outcome after 6 months; approximately 10 % of the patients die. Conversely, with malformations which scored I and II on the Spetzler and Martin table, surgical treatment has a good outcome in 96.5 % of the patients.

Bleeding due to an AVM therefore carries significant morbidity and mortality; there are therefore many good reasons for preventive treatment of "unruptured" AVMs.

Endovascular Treatment of Arteriovenous Malformations (AVMs) with Cerebral Hemorrhage

Bleeding caused by an AVM rupture is usually an intraparenchymal hematoma or an intraventricular spillage or a combination of the two. More rarely there is a subarachnoid hemorrhage, usually caused by the rupture of an associated aneurysm.

Unlike treating the rupture of an aneurysm, treating an AVM rupture is not traditionally considered an emergency, as it is believed that the probability of a second episode is more rare (it is estimated at 7–10 % in the first year).

However, we believe that there are some exceptions when the point of rupture is identified (usually represented by a pseudoaneurysm in a small branch relating to the AVM), especially in patients with intraventricular hemorrhage. Therefore, we deem it necessary to carry out an early angiographic study in all cases, especially when the patient's clinical conditions are severe (small bleeds which are clinically not very symptomatic are more often due to momentary fissuring of a draining vein, at a lower pressure than an arterial afferent).

If a pseudoaneurysm is detected, the lesion is excluded by endovascular treatment.

Procedure: preparation of the coaxial systems is the same as when treating an aneurysm, and it is the same as that used in almost all neurointervention treatments. However, the microcatheter is extremely thin and soft, so it can be transported by the blood stream which tends to drag it up into the branches related to the AVM.

If necessary, a coaxial microguide can be used, which in this case is also extremely soft and thin (about one-sixth of a millimetre). *Glue* is injected just off the pseudoaneurysm (a few millimetres at most). This liquid immediately polymerizes in contact with blood, and becomes solid.

The adhesive is a cyanoacrylate (n-butyl-cyanoacrylate), quite similar to the instant glue (crazy glue or super glue) commonly used in all homes. If the procedure is successful and eliminates the pseudoaneurysm, we believe the AVM can be considered an unruptured AVM. Therefore, it is possible to proceed with quieter timing, even with stereotactic radiosurgery treatment (gamma knife and cyber knife) when needed or indicated.

Cavernous Angioma

Cavernous angioma is considered a congenital disease, but there are elements that suggest it is an acquired disorder. There is a familial form, in which specific genes have been identified, and a sporadic form where there is no established

characteristic chromosomal framework. Furthermore, the familial form often presents multiple cavernous angiomas.

Cavernous angiomas are also called hidden malformations because they are not visible on angiography nor on CT scan when they do not have any calcifications. Therefore, the presence of a cavernous angioma must be suspected when the location of the bleed is not a typical one and the patient is young. MRI is the diagnostic procedure of first choice; T2 sequences detect the characteristic halo of haemosiderin.

These are low-pressure malformations, whose potential bleeding is less detrimental than the bleeding of an aneurysm or an AVM. Bleeding of a cavernous angioma is rarely fatal and rarely leaves serious permanent neurologic consequences because, rather than destroying the nerve fibres in the white matter, low-pressure bleeding dissociates them, and once the hematoma is reabsorbed, most of the symptoms also resolve.

Since cavernous haemangiomas may develop at any site of the central nervous system, the clinical manifestation and the risk of persistent neurological deficits are of course higher when the haemangioma is located (and bleeding) in an eloquent area. Typical examples are cavernous angiomas of the brain stem. The incidence of bleeding of this type of angiomas is higher and their bleeding also has very serious neurological manifestations in the acute phase, although in many cases the outcome may, after some time, not be as serious as one might expect because it is not destructive, but dissociative bleeding.

It is believed that once the angioma has bled, the chances of re-bleeding increase from 0.5 % per year for an "unrupted" cavernoma to 6% per year. Cavernous angiomas on the trunk seem to have a higher incidence of bleeding than in other locations.

Treatment is generally not urgent, since this kind of hematoma is hardly ever life-threatening. The main purpose of surgery is to prevent re-bleeding. It is preferable to wait for neurological conditions to be stabilized and for the oedema

associated with the bleed to reduce in size and then intervene after approximately 1 week or 10 days.

The general criteria for removing a cavernous angioma are:

1. It has bled.
2. It is surgically accessible.

Evaluating whether a cavernous angioma is surgically accessible in deep locations like the basal ganglia or brain stem depends on the experience of the surgeon [68]. Such operations are extremely complex and must be performed in highly specialized centres; it is not uncommon that what is judged as not surgically treatable in one hospital might be considered treatable in another one.

Surgery is feasible even on deep haemangiomas, but it requires experience and accurate intraoperative neurophysiological monitoring. This type of surgery is not performed in all neurosurgery centres. Surgery is to be recommended in experienced centres in order to avoid new episodes with potentially more severe outcomes.

It is advisable to avoid waiting too long (months) after the bleed because it is easier to operate when the hematoma is still fresh, when the cleavage plane is still preserved and before scar tissue forms, making removal of the cavernoma from the surrounding parenchyma more difficult. Given the location in the brain stem, it is of vital importance not to damage the surrounding tissue.

On the contrary, for supratentorial cavernous angiomas, which are in non-critical locations, the removal of a margin of surrounding tissue, corresponding to a haemosiderin flange visible on the MRI, helps reduce the risk of epilepsy in the post-operative period.

Dural Arteriovenous Fistulas (DAVFs)

The dural fistula is an acquired disorder which is believed to develop as a result of a focal inflammatory process, which generates a shunt between a meningeal artery and a pial vein. The process occurs in relation to the dural venous sinuses.

The presence of a direct shunt between artery and vein creates venous hypertension which may, depending on the structural characteristics of the venous drainage, carry a more or less severe risk of bleeding.

Symptoms can range from the subjective perception of a blow to cognitive impairment related to intracranial hypertension. Symptoms can typically evolve over years. Different rating scales have quantified the risk of bleeding from this pathology.

The Cognard scale [69] is the simplest one. It distinguishes 4 grades depending on the venous discharge, which might be:

1. In a dural sinus with physiological flow
2. In a dural sinus, partially thrombosed with retrograde flow into the pial veins
3. In a vein without dural discharge in dural sinus
4. In a dural vein that presents ectasia

The risk of bleeding increases with the score on the scale and reaches 40 % a year for grade 4. Venous engorgement or venous ectasia is the cause of the bleeding.

Extended dural fistulas may cause venous engorgement so as to generate intracranial hypertension, even without bleeding, causing progressive cognitive impairment.

Increased knowledge of the structure of dural fistulas led to the realisation that treatment of a dural fistula simply required closure of the venous shunt. The simple deafferentiation from the arterial side is inevitably followed by relapse. For many years this problem was treated surgically (technically simple surgery), but since the introduction of Onix, the treatment has essentially been endovascular.

It is essential that Onix goes beyond the site of the fistula and reaches and closes the venous side of the fistula. Treating fistulas types 1 and 2 (sinus) still causes difficulty when they affect a nonexpendable sinus. Endovascular techniques with Onix and balloon allow their evolution to be controlled.

Surgical treatment with simple interruption of vein drainage is limited to cases where endovascular access does not allow the point of the fistula to be reached safely or as a

result of incomplete endovascular treatments that preclude a subsequent endovascular approach [70].

Endovascular Treatment of Dural Arteriovenous Fistulas (DAVFs) with Cerebral Hemorrhage

DAVFs may result in intracranial hemorrhage when the fistula drainage vein is a cerebral vein (unlike a dural sinus) and bursts open because of the excessive arterial flow inside it.

Please note that a DAVF is a pathological arteriovenous passageway localized on the surface of a dura, almost always on the wall of a dural sinus. Arterial flow directly into the sinus results in sinus DAVF, which, depending on the severity, could cause simple hearing disorders or determine mental decline up to stupor and coma because of the progressive dysfunction of the whole intracranial venous system.

If the arterial flow enters a cerebral vein (or cerebellar) at its intersection with the sinus, but without being able to continue to the sinus, a countercurrent flow is generated in the cerebral vein. The vein can undergo progressive expansion up to a potential rupture.

As in all cases of intracranial hemorrhage after diagnosis via angio-CT and/or angiography, the lesion can be treated with an endovascular procedure. It is possible to heal a DAVF with drainage in a cerebral vein by occluding the first segment of the vein (the "foot" of the vein).

The procedure involves catheterization of arteries which are afferent to the fistula (usually a meningeal branch of external carotid artery) with microcatheters similar to those already described, up to a few millimetres from the site of the fistula.

A liquid material is then injected. Similar to *glue* but without its adhesive characteristics, it is a solution in which the solvent is dimethylsulfoxide (DMSO), which immediately and rapidly evaporates on contact with blood. The solute then precipitates and solidifies, occluding the vessel into which it is released.

The probability of success offered by this method is very high, exceeding 90 %. There may be some possible complications related mostly to thrombosis of the venous components even at some distance from the fistula.

1.1.6 Complications

Seizures

Seizures were observed in 4.2–20 % of ICH patients [23], with a risk of 8.1 % within 30 days after the onset of ICH. The ICH lobar location is the one most frequently associated with epilepsy [71].

Seizures should be treated immediately if they occur as they can worsen the prognosis, but there is no sure evidence to support the preventive use of antiepileptic drugs in ICH patients. Some studies indicate that antiepileptic therapy may be suspended 1 month after seizure, subject to an EEG examination.

Fever

Fever is an independent negative prognostic factor in ICH patients who survive the first 72 h [72], but there is no evidence that drug treatment improves the prognosis [73].

The external ventricular derivation catheters should be removed within 7 days because of the risk of infection.

Treatment of Hypoglycaemia

Elevated blood glucose values on admittance may be due to diabetes which is known or not properly understood or to stress-related hyperglycaemia, and they are associated with a significant increase in mortality. A study carried out on 992 ICH patients showed that hyperglycaemia on admittance (>9.2 mmol/L) in patients without diabetes resulted in a mortality rate four times higher than the mortality rate in patients

with normal blood glucose levels (<5.7 mmol/L) [74]. The optimum glucose target is unclear.

Deep Vein Thrombosis (DVT)

ICH patients are at high risk of suffering from thromboembolic disease; such risk is higher in female patients and in black people [23]. The CLOTS3 study has demonstrated the effectiveness of the use of intermittent pneumatic compression in reducing proximal DVT [75].

Indications for Monitoring Intracranial Pressure (ICP) in Hemorrhagic Stroke

The indication for monitoring intracranial pressure by means of intraparenchymal catheter or ventricular shunt is linked to the patient's clinical condition (GCS <8), mass effect of the bleed and evidence of cerebral oedema on brain CT scan [76].

Since there are no randomized studies on the monitoring and treatment of intracranial pressure in these patients, the indication for invasive monitoring, thresholds of intracranial pressure (<20 mmHg) and cerebral perfusion pressure (50–70 mmHg) are taken from studies carried out on traumatic brain injury (TBI) patients.

A limited number of cases show a possible role of elevated ICP in determining outcomes [77–79]. The catheter or ventricular shunt can be used in cases of acute obstructive hydrocephalus and IVH to drain blood from the ventricular system. In the latter case it can be used to administer fibrinolytic drugs directly into liquor [80]. Both acute hydrocephalus and the presence of intraventricular blood are in fact associated with a worse outcome [81, 82].

1.2 Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) is a spontaneous extravasation of blood into the subarachnoid space which occurs in the absence of trauma. It accounts for about 5 % of all strokes. This

disease mainly affects young people and it carries high mortality and disability rates [83], so that the social impact and loss of years of productive life are comparable to that resulting from cerebral hemorrhage and ischemic stroke [84].

Therefore, although it represents a small percentage of the total number of strokes, SAH is a major disease and a medical emergency, and it is a diagnostic and therapeutic challenge in emergency departments.

1.2.1 Epidemiology

The incidence of SAH is approximately 10 cases per 100,000 people per year with a range from 2 to 27 cases per 100,000 per year linked to the geographic areas under consideration. SAH is more common in Japan and Finland (22.7 and 19.7 cases per 100,000/year, respectively) and least frequent in China (2 cases per 100,000/year) and in Central and South America (4.2 cases per 100,000). In the United States and in Italy, the incidence of the disease is 9.7 and 10.8 cases per 100,000 per year, respectively [85, 86]. It is higher in black and Hispanic people than in white Americans [86].

In recent decades there has been a reduction of 0.6 % in the incidence of total SAHs, smaller than that observed for stroke in general [85].

The average age of SAH patients is lower than the age of patients suffering other types of stroke and, although the incidence increases with age, approximately 50 % of SAH patients are younger than 55 years [87]. In recent decades an increase has been observed in the average age of patients, from 52 to 62 years [88].

As far as gender is concerned, women have a slightly higher incidence than men (1.24 times), which is evident after 55 years and increases after that age [85, 88].

1.2.2 Aetiology

In 85 % of cases, SAH is secondary to spontaneous rupture of a cerebral aneurysm; in 10 % of cases it is an idiopathic SAH,

frequently located in the perimesencephalic area; in 5 % of cases it is due to rarer causes such as arterial dissection, arteriovenous malformations, dural arteriovenous fistulas, mycotic aneurysms, fusiform aneurysms, cerebral amyloid angiopathy, reversible vasoconstriction syndrome and vascular lesions in the spinal cord.

1.2.3 Risk Factors

The modifiable risk factors include active and passive cigarette smoking [89], high blood pressure and high alcohol consumption. Each of them doubles the risk of aneurysmal SAH (aSAH) [90]. Another risk factor is represented by the abuse of sympathomimetic substances (cocaine).

The non-modifiable aSAH risk factors are family history, understood as a first-degree relative having suffered an SAH, genetic diseases such as polycystic kidney disease with dominant autosomal inheritance, Ehlers-Danlos syndrome, deficiency of alpha-1-antitrypsin and female gender.

The risk of aSAH in women varies with age of menarche, pregnancies and menopause. Women who have had an early menarche, women who are going through menopause and first-time mothers have a higher risk of aSAH than other women. There is no evidence of increased risk in pregnancy, childbirth and the postpartum period [91, 92].

People with a family history of SAH tend to be younger than those with sporadic SAH and have larger and multiple aneurysms [93, 94].

The risk of SAH increases in the presence of large unruptured aneurysms of the posterior circulation, particularly if symptomatic, and in the presence of previous SAH with or without untreated residual aneurysm, as demonstrated by the long-term follow-up of ISAT study [95].

The International Study of Unruptured Intracranial Aneurysms (ISUIA) study has provided information on the risk of aneurysm rupture in relation to the location and size of the aneurysm. It is higher for aneurysms of the anterior

communicating artery and of the basilar artery apex as compared to the middle cerebral artery.

For aneurysms with a diameter of less than 7 mm, the risk of rupture is low (approximately 0.1 % per year) and progressively increases as the size increases. In the study, 75 % of unruptured aneurysms had a diameter of less than 1 cm. Larger aneurysms (>8 mm) longitudinally followed by MRI tend to grow more over time and therefore they are at greater risk of rupture [96].

Also, the morphological characteristics of the aneurysm, such as a bottle-shaped neck and the relationship between the size of the aneurysm and the afferent vessel, are associated with the risk of rupture [97–99] but it is still unclear how to decline such information for individual patients to predict the risk of SAH.

A model has recently been developed derived from the analysis of six cohort studies, which has led to the creation of a map of the risk of rupture of an intracranial aneurysm [100]. The identified predictors of aneurysm rupture are age, high blood pressure, history of SAH, size of aneurysm, location of aneurysm and geographic area. They form the PHASES score which corresponds to a precise risk of rupture at 5 years [100]. According to this score, the risk of rupture of an aneurysm at 5 years varies from 0.25 % in patients below the age of 70 without vascular risk factors and with small aneurysms of the internal carotid artery (<7 mm) to over 15 % in individuals older than 70 with hypertension, a history of SAH and giant aneurysms (<20 mm) of the posterior circulation. In the Finnish and Japanese population, the risk increases by 6.3 and 8.2 times, respectively.

Some studies have demonstrated a connection between diet and SAH. In particular, high consumption of vegetables is associated with a reduced risk of aSAH [101].

The factors that precipitate the rupture of an aneurysm have not yet been clarified, but it is assumed that a sudden increase in transmural pressure can play a role. Some studies have found that activities such as physical exercise, sexual activity and stress precede the occurrence of aSAH in over

20 % of the cases; no triggers have been identified for the remaining 80 % of the cases [89, 102, 103].

1.2.4 Prognosis

The prognosis is severe and the death rate, although it has decreased by 17 % in recent decades thanks to improvements in the management of SAH in hospitalized patients [88, 104], still remains high, reaching 45 % at 30 days in some studies [105].

A meta-analysis of population studies showed a geographical variation in median mortality rate, significantly lower in Japan (27 %) as compared to Europe (44 %), the USA (32 %), Asia excluding Japan (38 %), Australia and New Zealand [88].

In population studies, 12–15 % of SAH patients die before reaching the hospital (at home or during transportation) and 25 % of the remaining patients die within the first two weeks after the event [88, 106].

More than a third of the survivors remain disabled and typically some cognitive deficits are observed, such as impaired memory, executive functioning and attention disorders that impact on daily life [83]. Cognitive deficits tend to improve during the first year; however, they persist in approximately 20 % of patients [107], leading to a low quality of life.

Nineteen percent of patients show residual disability in conditions of dependence 3–12 months after the event [88].

Deterioration of the clinical condition is due to the initial severity of the bleed and/or to the onset of complications such as re-bleeding and late ischemia.

Re-bleeding can also occur very early. In 15 % of cases early clinical deterioration is caused just by re-bleeding that occurred before the first CT scan or before the patient entered the hospital, and it accounts for pre-hospital mortality.

The risk of re-bleeding is higher in the first 24 h after the aSAH, with a peak in the first 6 h; [108] after the first day, the

risk of untreated aSAH remains high in the following 4 weeks, reaching 30 % in a month and decreasing gradually from 1 to 2 % per day to around 3 % per year [109]. The prognosis after re-bleeding is severe, with 60 % mortality rate and residual disability in 30 % of cases [110].

Delayed cerebral ischemia occurs in about one third of cases, mainly in the first and second week after the aSAH (peak 4–12 days). About 25 % of patients die and 10 % are disabled.

Negative prognostic factors include advanced age, clinical severity at admission and the extent of bleeding visible on the CT scan.

Other negative prognostic factors are: ruptured aneurysms of the posterior circulation, large diameter aneurysm and more recently the Apo E lipoprotein allele ε4 [111, 112]. Clinical severity and in particular the level of consciousness are the most important prognostic factors.

Perimesencephalic Nonaneurysmal Hemorrhage

This type of SAH is confined to perimesencephalic cisterns, generally in the anterior portion of the midbrain and the pons, although sometimes it may be limited to the quadrigeminal cistern [113, 114]. The condition is defined by the characteristic distribution of subarachnoid bleeding and by a normal angiography, necessary for excluding the presence of an aneurysm.

The prognosis of perimesencephalic SAH is good, there is no risk of re-bleeding in the short and long term and the only complication that may occur is hydrocephalus [113].

Perimesencephalic SAH also presents with severe headache but the onset of symptoms is more gradual than in aneurysmal SAH (peaking in minutes rather than seconds). The clinical condition of patients are milder, they sometimes appear slightly disoriented but there are no changes in vigilance [115, 116].

The cause of bleeding is not known, but it is assumed to be of venous origin. Milder symptoms, less rapid onset of

headache, limited bleeding and absence of aneurysms support this hypothesis [113].

1.2.5 Clinical Presentation

Spontaneous SAH typically manifests with an unusually severe headache that is generally widespread and has a sudden onset. The so-called thunderclap headache is often described as "an explosion" because of the intensity and speed of onset of pain, with peak time from a fraction of a second to a few seconds in 75 % of cases [116]. However, what should raise the suspicion of SAH is not only the intensity of the pain but its mode of onset. The headache might be associated with an altered state of consciousness, focal neurological deficits and vomiting, but in a third of all cases, the headache is the only symptom. In up to 77 % of cases, the headache is accompanied by photophobia, nausea and vomiting [117]. These are not SAH-distinctive characteristics because they are present in about half of patients suffering from thunderclap headache which is not associated with SAH [116].

Impaired state of consciousness is frequent. It was observed in 53 % of 109 patients in a retrospective study [118] and in about two-thirds of 346 patients on arrival at the hospital in a prospective study; approximately half of them were in a coma [119]. The normal state of consciousness may be recovered or it may remain altered.

Rarely, the patient with SAH may present with an acute confusional state (1–2 % of cases) [120].

Focal neurologic deficits are detectable in 10 % of cases and are due either to the extension of the bleeding in the brain parenchyma or to focal cerebral ischemia which is secondary to acute vasoconstriction occurring immediately after rupture of the aneurysm.

The deficits vary in relation to the bleeding site. The complete or partial deficit of the third cranial nerve has a

localizing value because it is the sign of a ruptured aneurysm typically located at the level of the internal carotid artery, at the origin of the posterior communicating artery. The deficit of the sixth cranial nerve, when present, has no localizing value.

A stiff neck is a common sign and is due to an inflammatory response to the blood present in the subarachnoid space. It does not appear immediately after the bleed but needs 3–12 h to occur and cannot be present in patients in deep coma and with negligible SAH [121]. Therefore, the non-accrual of neck stiffness does not exclude SAH.

Seizures on onset have been reported in 7 % of SAH patients [116, 122, 123] and are strongly indicative of SAH caused by aneurysm rupture, since they have not been described in patients with perimesencephalic SAH or in patients with thunderclap headache without bleeding [116].

It should be remembered that although the typical presentation has been described, SAH patients may show isolated headaches and a normal neurological examination. Presentation and severity of the headaches can vary, which may make diagnosis difficult [124].

Some studies have shown that 10–43 % of patients diagnosed with SAH presented a so-called "sentinel" headache from 2 to 8 weeks before the major bleed [125, 126]. Such headache is often milder than that which occurs with the major rupture and may persist for days; it may be associated with nausea and vomiting, but meningeal signs are rarely present. In the absence of a proper diagnosis, a major re-bleed is very frequent in the following days or weeks.

Therefore, it is necessary to maintain a high degree of clinical suspicion for the disease, which should be excluded by appropriate diagnostics, since a missed diagnosis is associated with mortality and disability rates at 1 year that are four times higher in patients with minimal or no neurological signs at the initial examination [124]. The necessary examinations must be carried out on all patients struck by an

unusual headache with acute onset and/or unusual pain characteristics.

It should not be forgotten that SAH accounts for only about 1–3 % of all visits to the emergency room for acute headache [127].

The headache lasts 1–2 weeks, though sometimes it can last longer; the minimum duration of the headache is unknown [113].

SAH patients may present intraocular hemorrhages of all types: retinal, subhyaloid or vitreous. In a systematic review vitreous hemorrhage was observed in 13 % of aSAH patients and was more frequent in subjects with an impaired state of consciousness [128]. Intraocular hemorrhage is due to increased intracranial pressure that causes obstruction of the venous drainage of the central retinal vein when it crosses the optic nerve sheath. Linear or flame-shaped subhyaloid bleeds are visible in the vicinity of the optical disc and may extend into the vitreous to configure Terson's syndrome. Patients may complain of a brown stain that obscures the view. The examination of the fundus oculi is essential in these patients.

SAH clinical severity is expressed by means of rating scales.

1.2.6 Acute-Phase Management

Pre-hospital phase management should include vital sign detection, assessment of the level of consciousness, including determination of the Glasgow Coma Scale (GCS) score, and a brief neurological assessment to detect focal neurological deficits by means of a formal scale in order to assess the severity of the symptoms. The patient must be stabilized, and, depending on the patient's clinical condition, airway management must be performed.

Cardiac arrest occurs in 3 % of cases and it is important to perform cardiopulmonary resuscitation (CPR) because half of the survivors recover their independence [129].

1.2.7 Assessment in Emergency

A typical candidate for SAH diagnostic protocol is a patient presenting with severe headache of sudden onset. The headache is typically described by the patients as the worst of their lives, with a peak time of seconds and associated with nausea, vomiting and focal deficits. Most severe headaches have a benign cause; approximately 10–16 % are caused by a serious medical condition, including SAH. It is more difficult to decide when to be alarmed in subjects with a vague modification of the primary headache they suffer from and with a normal neurological examination.

Patients presenting with acute headache of sudden onset should undergo brain CT scan if any of these conditions are present: age >= 40, neck pain or stiffness, witnessed loss of consciousness, onset during coitus, thunderclap headache and neck stiffness at neurological examination. This decisional scheme has a 100 % sensitivity for diagnosis of SAH [130].

1.2.8 Instrumental Diagnostics

In case of suspected SAH, a brain CT scan without contrast is the first examination that must be performed, but CT scans have some limitations, related mainly to the time when the examination is carried out and the amount of bleeding. A CT scan guarantees a high level of sensitivity (95–99 %) in detecting blood in the subarachnoid space within the first few hours of onset of symptoms, i.e. in the first 24 h; such sensitivity progressively reduces as time goes by (over the following days) because of the degradation of the blood and its dilution secondary to the continuous circulation of cerebrospinal fluid [131–134].

Within the first 6 h from onset of headache in patients with suspected SAH, the sensitivity of a CT scan is 98.5 % (95 % CI 92.1–100 %) [135]. The predictive negative value of CT results is almost 100 % (95 % CI 99.5–100 %) if the exam is carried out with third-generation CT scans and interpreted

by neuroradiologists or radiologists experienced in reading Brain CT scan images [134]. This result was confirmed by a recent retrospective study in non-academic centres (negative predictive value 99.9 %; 95 % CI 99.3–100.0 %) [136]. Over the 6 h following onset of headache, sensitivity is reduced to 90.0 % (95 % CI 76.3–97.2) [135].

MRI might have the same sensitivity as CT in detecting SAHs in the first two days after the event [38] but may be more sensitive in the following days when the hyperdensity on a CT scan is reduced. The use of sequences with fluid-attenuated inversion recovery (FLAIR) and SWI is particularly sensitive to paramagnetic substances such as haemoglobin degradation products [137].

If CT scan findings are negative and clinical suspicion is high, a lumbar puncture should be performed, taking into account that in only 3 % of patients with negative CT findings within 12 h of onset of symptoms, a lumbar puncture shows haemoglobin metabolites and an angiography confirms the presence of a ruptured aneurysm [132]. Account must also be taken in the negative predictive value of a third-generation CT carried out within 6 h of the onset of symptoms.

A lumbar puncture should be performed at least 6 h after the onset of symptoms and preferably 12 h afterwards. In fact, if the cerebrospinal fluid (CSF) is obtained early and contains blood, it is almost impossible to discriminate between blood actually present in the subarachnoid space and blood generated by a traumatic puncture.

If correct timing is observed, blood degradation products will be present only in the case of a hemorrhage; in particular there will be bilirubin resulting from fragmentation of erythrocytes in CSF [113, 138]. The three-tube test carried out in order to differentiate the presence of blood resulting from a traumatic puncture from the presence of blood in subarachnoid space is not reliable [139].

There are specific technical recommendations for CSF analysis when SAH is suspected, and the recommended method is spectrophotometry with quantitative analysis of bilirubin.

An increase of bilirubin in the CSF indicates the presence of blood in the subarachnoid space and excludes that it is due to a traumatic puncture. The increase in bilirubin is generally accompanied by the presence of oxyhaemoglobin; the isolated presence of oxyhaemoglobin is almost always an artefact but may occasionally occur in SAH [140].

The absence of oxyhaemoglobin and bilirubin does not support diagnosis of SAH. It is not advisable to proceed directly to a vascular imaging exam (CT angiography or MRA) before demonstrating the presence of SAH, as unruptured aneurysms with diameters of <5 mm could be detected, which are to be considered incidental findings [113].

A recent study has shown that CT scans and CT angiograms detect aneurysmal SAH in 99 % of cases [141] and lumbar puncture remains the correct approach.

Bleeding resulting in a ruptured aneurysm cannot be confined to the subarachnoid space and may extend to the brain parenchyma, the ventricular system and the subdural space.

An intraparenchymal hematoma has a localizing value for the ruptured aneurysm: frontal or fronto-basal hematomas in anterior communicating artery aneurysms, temporal area hematomas for posterior communicating aneurysms and hematomas in situ for middle cerebral artery aneurysm. The possibility that an intraparenchymal hematoma is secondary to the rupture of a cerebral aneurysm varies from 4 to 35 % of cases.

Identifying Location of the Bleed

Digital angiography has always been considered the gold standard for identifying the aneurysmal site of a bleed. Currently CT angiography has become the rule even if it might not identify small aneurysms. The sensitivity and specificity of CT angiography depend on the execution method and on the experience of the professional who interprets it, being, respectively, 90–97 % and 93–100 % [142–144].

The advantages of CT angiography are linked to the fact that it can be performed quickly and immediately after a CT scan which shows the presence of SAH. In many patients, the decision regarding the type of treatment of the aneurysm – endovascular or surgical – is made on the basis of CT findings. Most unidentified aneurysms on CT angiography have a diameter of less than 4 mm [145].

CT angiography and MRA angiography have the same sensitivity for aneurysms. MRA is used to study unruptured aneurysms and for screening patients at high risk of aneurysm, since it does not involve using radiation and contrast medium; vice versa, it is rarely used in the acute phase when the patient may not be very cooperative. MRA has two disadvantages: it requires more time than CT angiography and it is rarely found in emergency departments.

In patients with SAH, cerebral angiography is indicated even if no aneurysm has been revealed in a noninvasive examination. It is used also to plan the type of aneurysm treatment (embolization or microsurgery).

If cerebral angiography findings are negative, the exam should be repeated a week after symptom onset, as it could detect aneurysms which went undetected in the acute phase because of thrombosis of the aneurysm or immediate destruction of the aneurysm at the moment of rupture (when they are small) or local or widespread vasospasm. In 1–2 % of cases, aneurysms are detected in the second angiography exam.

If the second angiography findings are negative, the exam should be repeated after 1–3 months. Cerebral angiography is an invasive examination and it is not risk-free; the risk of temporary or permanent neurological complications in SAH patients is 1.8 % and the risk of re-bleeding of the aneurysm during the exam is quite low [146].

It should be remembered that cerebral angiography, in the case of SAH which is compatible with the rupture of an aneurysm of the posterior circulation, must include the study of both vertebral arteries since aneurysms which are localized on the posterior-inferior cerebellar artery or other proximal

branches of the vertebral artery might not be highlighted if only one vertebral artery is studied.

In 10–15 % of cases, the causes of bleeding are not identified. Such SAHs are defined as SAH sine materia or more properly as SAH with negative angiography. Most of these cases fall within the category of nonaneurysmal perimesencephalic SAH of venous origin.

If the angiography is negative in the acute phase, an MRI should be performed to exclude a cervical disease that might have originated the SAH [147].

1.2.9 Rating Scales

As previously mentioned, neurological severity on admission, age, amount of bleeding and endoventricular extension of bleeding are prognostic factors for outcome after SAH.

Among these factors, the neurological status of the patient on admission is the most important and can vary over time. In order to have standardized assessment, it is necessary to have a valid and reproducible assessment tool, having good correlation with prognosis and good interobserver agreement.

Three rating scales are basically used to assess SAH: the Hunt and Hess scale, the World Federation of Neurological Surgeons (WFNS) scale and the modified Fisher scale (see Appendix). These scales have been created for different reasons, none of which are strongly related to the prognosis.

The Hunt and Hess (HH) scale was created in 1968 to stratify patients in relation to the surgical risk [148] and is still widely used. It takes into account the level of consciousness, intensity of headache, neck stiffness and severity of focal deficits. The categories are not clearly defined, however, and the scale has low levels of reproducibility and validity [149, 150].

The World Federation of Neurological Surgeons scale was proposed in 1988 by a commission of the WFNS in an attempt to identify a valid and reproducible tool [151]. It is based on the Glasgow Coma Scale (GCS), which has the advantage of having good interobserver agreement [152–154], and a grade has been added to levels 13 and 14 to insert the

presence or absence of focal neurological deficits. The scale is easy to use but the correlation between each grade and the prognosis is controversial, and the cut-offs within the scale are based on consensus and not on a formal assessment.

Another scale was later proposed, based solely on GCS: the Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage (PAASH) Scale [155]. This scale is divided into five categories and the cut-offs between them are different from the WFNS cut-offs. In fact, the PAASH cut-offs have been selected by calculating the point at which two consecutive categories correspond to a statistically different prognosis at 6 months. This scale has good internal and external validity [156].

In the HH, WFNS and PAASH scales, the higher the score, the worse the patient's prognosis. A study which evaluated the prognostic accuracy of the three scales showed that the WFNS and PAASH scales have a good prognostic value. The PAASH scale seems to have a more linear and gradual correlation with the risk of poor prognosis in the higher categories than the WFNS scale, and every increase in grade relates to a poorer prognosis [156] (See Appendix).

The interobserver agreement is similar in the WFNS and PAASH scales (weighted kappa values: 0.60, 95 % CI 0.48–0.73, and 0.64, 95 % CI 0.49–0.79, respectively), while it is lower for the HH scale (weighed kappa values: 0.48, 95 % CI 0.36–0.59) [157].

The modified Fisher scale is based on CT findings and derives from the original Fisher scale. It was developed in order to better predict the risk of angiographic vasospasm. The correlation is linear: the higher the score, the higher the risk of angiographic vasospasm [158, 159] (See Appendix).

Another scale has recently been proposed to stratify the risk of cerebral ischemia: the VASOGRADE scale. It combines the WFNS scale and the Modified Fisher Scale (VASOGRADE green, grade 1 or 2 on the modified Fisher scale and WFNS 1 or 2; VASOGRADE yellow, grade 3 or 4 on Modified Fisher Scale and WFNS 1, 2, or 3; VASOGRADE red, WFNS 4 or 5) [160].

1.2.10 Treatment of the Acute Phase and Complications

Emergency treatment includes airway management, close haemodynamic monitoring, support treatment, prevention and treatment of complications. This may require rapid transfer of the patient to a tertiary centre to secure the aneurysm.

The number of clinical interventions is limited in SAH patients, but it has been shown that by treating patients in specialized centres that have a large volume of patients and multidisciplinary teams, their prognosis improves [161, 162]. "Large volume" is intended as at least 35 cases per year, with best benefits found in centres that treat more than 60 cases/year; in general, the higher the number of cases treated, the better the prognosis [163, 164].

Patients who survive the early hours are struck by three major complications: re-bleeding, delayed ischemia and hydrocephalus. In addition, there may be systemic complications that have a negative impact on prognosis.

Re-bleeding

Re-bleeding is a serious complication that significantly worsens the patient's prognosis [165] and is probably related to the dissolution of the clot by natural fibrinolysis at the site of aneurysm rupture. The risk of re-bleeding occurs in 4–15 % of cases during the first post-bleed days and decreases gradually over the next 2 weeks [166, 167]. There are no more incidences of it once the aneurysm is secured [168].

Aneurysm Treatment

The most effective treatment to reduce the risk of re-bleeding is early exclusion of the aneurysm from the circulation causing the bleed. Treatment of the aneurysm can be either endovascular or surgical, by positioning a clip on its neck.

Endovascular treatment has the advantage of avoiding craniotomy and allows more rapid recovery after the procedure, but it needs angiographic follow-up because there is a risk of the aneurysm reopening due to coil compaction.

The choice of treatment is based on the location and morphology of the aneurysm neck. Middle cerebral aneurysms or aneurysms localized on tortuous vessels are treated surgically because of the difficulty in reaching them intravascularly, while endovascular treatment is easier with deep posterior circulation aneurysms. Patients with comorbidities are more often delivered endovascular treatment.

Endovascular Treatment of Aneurysms in Emergency

Endovascular treatment of aneurysms in emergency was introduced into clinical practice in the early 1990s and has gradually consolidated to become the treatment of choice in most cases. Some exceptions still remain.

Once satisfied that the bleeding episode was caused by the rupture of an aneurysm, and once the bleeding aneurysm has been identified by means of a CT angiography or an angiographic study, the usual approach is to intervene as soon as possible and usually in the first 24 h to prevent a further rupture, which is highly probable (about 30–40 % in the first weeks with peaks in the first few days).

Endovascular treatment is performed through catheterization of cerebral vessels, starting from the femoral artery (usually the right one for the logistics of the equipment). In extremely rare cases, access is achieved through direct puncture of the carotid artery, usually when femoral access fails.

The procedure is carried out by inserting coaxial catheters (one inside the other). A first tube, called the introducer (usually 2.5 mm calibre and 15 cm in length), is inserted into the femoral artery. The tube contains a guide catheter approximately 90 cm long and calibre 6 French (6 French = 2 mm), which is sent into the internal carotid or vertebral artery, up to a height corresponding more or less to the second-third cervical vertebra.

Inside the guide catheter, there is a microcatheter of submillimetre calibre, which is fed up into the aneurysm. Such navigation of the cerebral arteries is usually done with the help of a microguide: a very thin metal wire with a curved tip that can be rotated in different directions (and then subsequently pushed into the desired branch). It is located within the microcatheter.

Once the aneurysm is reached, a platinum metal wire (spiral or coil) can be pushed into the microcatheter. The wire has "winding shape memory" which allows it to return to a three-dimensional ball of the desired size, corresponding to the size of the aneurysm.

Several well-compacted spirals are usually needed to completely exclude the aneurysm sac, but if the aneurysms are very small one spiral is enough. The ultimate goal of the procedure is to completely exclude the aneurysm from the circulation (to prevent further ruptures) and to maintain perfect patency of all the arteries in the region.

All intracranial aneurysms may receive endovascular treatment, but not all with the same level of safety and simplicity. In particular, aneurysms at the bifurcation of the middle cerebral artery (for which a surgical approach gives the best results), wide-necked aneurysms (requiring the help of other procedural tools like balloons or stents) or dissecting aneurysms (which may also require the use of stents or in some cases the occlusion of the artery on which they are located).

Endovascular treatment of ruptured aneurysms has significantly improved over time, but in essence the basic technique has always remained the original one, which was developed by Italian physician Dr Guido Guglielmi in the early 1990s (the first coils, which are still available, were called GDCs: Guglielmi Detachable Coils). This technique has a very high success rate (above 90 %) and peri-procedural complications account for 7.4 %. Complications are mainly ischemic, due to the occlusion of arterial branches in the area of the aneurysm or of emboli in distal vessels. Mechanical aggression on the aneurysm via the insertion of catheters, guides or spirals, may break it down.

The randomized controlled International Subarachnoid Aneurysm Trial (ISAT) showed that in patients eligible for both treatments, endovascular treatment reduced the probability of poor outcome at 1 year (reduction in the absolute risk of mortality and disability: 7 %), against an increased percentage of re-bleeding 1 year after the intervention [169].

In the ISAT study, complete occlusion of the aneurysm at the first angiographic follow-up was lower in the group submitted to endovascular treatment compared to the group treated with surgery (66 % vs 82 %). Subgroup analysis showed a reduction in the absolute risk of poor outcome by 27 % for posterior circulation aneurysms (95 % CI 6–48 %) and by 7 % (95 % CI 3–10 %) for anterior circulation aneurysms.

The observed early benefit of endovascular treatment is maintained in the long term, although it reduces over time. The 5-year mortality is significantly lower in the endovascular group compared to surgery (11 v 14 %, RR 0.77, 95 % CI 0.61–0.98; $p = 0.03$), but among those living 5 years, there were no differences between the two treatment groups with reference to independence (83 % endovascular and 82 % neurosurgical) [95].

Note that the mortality rate in patients with SAH from a treated ruptured aneurysm, conditional on survival at 1 year, had increased compared to the general population (1.57, 95 % CI 1.32–1.82; $p < 0.0001$) [95].

Endovascularly treated patients must be checked at 6 and 12 months in order to identify any inadequate occlusions due to coil compaction and subsequent rehabilitation aneurysm with risk of bleeding [168]. Although small, the risk of re-bleeding after the first year remains higher in endovascularly treated patients than in surgically treated patients (10 vs 3 cases, log rank $p = 0.06$) [95].

Note that there were 11 more cases of bleeding secondary to ruptured aneurysms, which were different from the initial one treated; in six cases, bleeding was secondary to aneurysm ruptures that had not been present on previous angiographic exams and therefore had to be considered de novo. The

external validity of the study, however, was relatively low, given the high number of patients excluded. Furthermore, the majority of the patients involved in the study had a low WFNS score (grades 1–2 in approximately 80 % of patients, grade 3 in 6 % of cases), that is to say, the patients were in good clinical condition and had small aneurysms (<5 mm in over 50 % of cases).

Only 7 % of aneurysms had a diameter of over 10 mm and middle cerebral artery aneurysms were underrepresented. Therefore, it remains debatable which is the best treatment of larger aneurysms (10 mm in diameter) and of middle cerebral artery aneurysms.

A Finnish study did not observe any statistically significant differences between the two types of treatment at 1 year and at 39 months [170]. The Barrow Ruptured Aneurysm Trial showed a better prognosis at 1 year in patients treated endovascularly compared to those treated surgically, but after 3 years this difference was no longer evident [171, 172].

The Cochrane meta-analysis shows that if patients are in good clinical condition after aneurysmal SAH, and the aneurysm is considered eligible for either surgical or endovascular treatment, the latter is associated with a better prognosis in the short and long term and therefore must be the treatment of choice [173].

Re-bleeding occurs after a median time of 3 days from treatment and rarely after 1 year; the greatest predictor of re-bleeding is the incomplete obliteration of the aneurysm [174]. At follow-up in the long term, all re-bleeding after endovascular treatment occurred within 5 years from the initial event; bleeds occurring after more than 5 years were caused by aneurysms which were different from the one initially treated. In one single case a re-bleed was caused by a surgically treated aneurysm.

This data suggests that the risk of re-bleeding is not constant over time, but this hypothesis must be confirmed by other observations. A new, later endovascular treatment (more than 3 months after the first treatment) was performed in 9 % of embolized patients, significantly more frequently

than in the surgical group (HR 6.9; 95 % CI 3.4–14.1); this did not result in changes in the prognosis measured with the mRS.

Two other randomized trials completed the recruitment: the HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS), which compared hydrogel-coated coils with platinum bars, and the Cerecyte Coil trial, which compared spiral polymer-loaded coils with platinum standard coils.

Surgical Treatment

These days, the decision on how to treat a brain aneurysm should be made in close collaboration with an interventional neuroradiologist.

Following the publication of the ISTAT study in 2005 [168, 169], it became clear that the endovascular treatment of cerebral aneurysms prevails. In fact, this study found that endovascularly treated patients benefit overall slightly more than those treated surgically.

Since endovascular treatment is certainly less invasive than the surgical approach, it has currently become the first treatment of choice. However, this is not a concept that can be applied to all aneurysms. The morphology of some aneurysms makes them more suitable for endovascular treatment; the location and morphology of other aneurysms make them more suitable for surgical treatment.

Generally speaking, the criterion leading to endovascular treatment is the presence of a tight-neck aneurysm or an aneurysm located on proximal vessels or in the posterior circulation, while broad-based or more superficial anterior circulation aneurysms have a better outcome when treated surgically.

It is essential that there is a good parity of skill and experience between the surgeon and the interventional radiologist of the centre where the patient is treated, in order to avoid poor clinical choices due to the lack of expertise of one of the two team members. Unfortunately, these days the availability of skilled vascular surgeons is decreasing following the

spread of endovascular treatment, and this phenomenon is likely to further increase the imbalance.

Surgical techniques have evolved over time, making treatments less and less invasive. Today an aneurysm can be treated with a few centimetres of surgical incisions without cutting the patient's hair.

In the case of subarachnoid hemorrhage, the presence of hydrocephalus must immediately be evaluated, and the first surgical procedure most often performed is the placement of an external ventricular derivation. Blood inside the subarachnoid space often creates an obstacle to re-absorption of cerebrospinal fluid resulting in hydrocephalus.

1. *Hydrocephalus*
   If the CT scan already shows hydrocephalus, external ventricular drainage must be put into place before performing an angiography.

   Hydrocephalus is the most common early complication of SAH and occurs in approximately 20 % of patients [175]. In cases where there is a neurological deterioration due to hydrocephalus, an external ventricular derivation must be put into place. Drainage of the cerebrospinal fluid leads to improved neurological conditions in more than 30 % of the patients with poor-grade aneurysmal SAH [176].

   Literature does not confirm an increased incidence of re-bleeding following the placement of a ventricular catheter, if it is positioned correctly. Avoiding even a few hours of elevated intracranial pressure during angiography or possible embolization improves the patient's outcome.

2. *Hematoma*
   The extension of intraparenchymal bleeding due to the rupture of an aneurysm occurs in one case out of three [113]. If the CT scan shows a hematoma with mass effect causing shifts of the intracranial structure or of the midline, surgical evacuation of an expansive process is indicated, rather than the endovascular option. The aneurysm will then be treated during the same intervention. If the aneurysm is too complex or too deep to be treated surgically,

endovascular treatment may be indicated as a second option and certainly at greater risk for the patient.

*A subdur*al hematoma is rarely associated with SAH (2 % of cases) [177], but it must be removed if it is detrimental to life. Intraventricular extension is associated with poor prognosis. Observational studies have shown that the placement of an external ventricular catheter is not useful, but may be more promising when combined with intraventricular fibrinolysis [178, 179].

3. *Treatment of the aneurysm*
   Surgical treatment of aneurysms requires surgical experience and therefore not all neurosurgeons are able to treat them (and in the future there will be fewer and fewer) [180].

Given the tendency to re-bleed in the first hours after the intervention, it is appropriate that the treatment is carried out as quickly as possible, without however operating late at night (it is proven that operations performed late at night have more complications than those performed during the day) [181]. In most neurosurgery departments therefore, if a ruptured aneurysm requires surgical treatment after midnight, it is stabilized and operated on in the morning [182].

The distinction between early and late surgery, which has characterized a lot of the literature on the timing of treatment, has today lost its meaning. It is essential to secure the aneurysm from re-bleeding by excluding the aneurysm as soon as possible from the circulation.

The surgical procedure, which today is becoming less and less invasive, generally requires a craniotomy for most aneurysms of the anterior circulation, in the frontotemporal region, and the gradual exposure of the segment of the circle of Willis concerned, using the operating microscope, to expose the neck of the aneurysm. It may be necessary to use clips on feeding vessels to temporarily reduce the flow in the aneurysm, if the size of the aneurysm prevents correct exposure of the feeding vessels. Finally, the aneurysm is excluded by placing one or more clips at its base, on the neck. The surgeon aims to close the aneurysm without rupturing it and

to maintain the flow in the vessels on which the aneurysm is placed, without clipping them.

Sometimes it may be technically very difficult because of the size of the aneurysm, the arrangement of the vessels, the presence of atheromatous plaques on the base of the aneurysm, the presence of thrombi within the aneurysm, the fragility or the wall of the aneurysm adhering to the parenchyma.

While exposing and isolating the aneurysm, very close cooperation with the anaesthesiologist is needed in order to keep blood pressure under control.

After the aneurysm has been closed, the patient is generally treated in an intensive care unit [183].

The next steps after SAH and intervention are just as important as the treatment of the aneurysm. There is the possibility that, unless treated preventively, vasospasm may occur in the following days (from the third day and peaking between the seventh and the tenth), which can lead to ischaemic damage that may also be very disabling.

Today, preventive treatment with calcium antagonists (nimodipine) has significantly reduced morbidity related to vasospasm [184]. Nevertheless, young patients with a lot of blood in the base cisterns have a high risk of developing vasospasm. Daily monitoring of the flow rate of intracranial vessels via transcranial Doppler helps to detect vasospasms in the early stages and to treat it aggressively while it is still modest. When the spasm is severe, the effectiveness of the treatment is reduced.

Medical Treatment of Re-bleeding

(a) Antifibrinolytic therapy
After the rupture of the aneurysm, a fibrin clot covers its wall, in contact with the blood inside it and with the subarachnoid space outside. The adjustment factors of fibrinolysis play an important role in re-bleeding. Antifibrinolytic therapy should reduce the risk of re-bleeding by reducing the endogenous fibrinolytic activity and preventing clot lysis.

Tranexamic acid, epsilon amino-caproic acid or other equivalents are antifibrinolytic drugs. Systemic administration of antifibrinolytic drugs has been the subject of many studies; parallel to a decrease in the number of episodes of re-bleeding, there is certainly a higher incidence of delayed ischemia, in particular for administrations prolonged for over 72 h [185, 186]. The Cochrane meta-analysis, which evaluated the efficacy of antifibrinolytic therapy, included ten studies with a total of 1904 patients. The results demonstrate that antifibrinolytic therapy significantly reduces the risk of re-bleeding (RR 0.65, 95 % CI 0.97–0:44); however, it neither reduces mortality (RR 1.00, 95 % CI 0.85–1.18) nor improves the prognosis (death, vegetative state and severe disability: RR 1.0, 95 % CI 0.91–1.15) [187]. The lack of effectiveness in prognostic terms may be due to the significant increase in the risk of ischemic stroke (RR 1.41; 95 % CI 1.4–1.91, 83 per 1000 participants). No effect of the therapy has been observed on the rate of hydrocephalus in five studies that have considered this aspect (RR 1.11, 95 % CI 0.90–1.36).

When antifibrinolytic therapy is associated with strategies for the prevention of cerebral ischemia, the prognosis does not improve ("poor outcome": RR 0.85, 95 % CI 0.64–1.14; mortality: 0.8; 95 % CI 0.52–1.35), although there is no increased risk of ischemic stroke (RR 1.9, 95 % CI 0.78–1.51) [185].

Precocious intravenous infusion of antifibrinolytic (tranexamic acid 1 g intravenous in 10 min, followed by 1 g every 6 h) seems to have a protective effect for up to a maximum of 24 h, before the aneurysm may be secured. A multicentre study is currently underway to test this hypothesis [188].

(b) Blood pressure treatment

When the aneurysm is not secured, any changes in cerebral blood flow and intracranial pressure can theoretically promote re-bleeding. Several factors have been associated with this: size of the aneurysm [189], severity of the clinical picture (WFNS 4–5), severity of the initial radiological

clinical picture (mFisher 3–4) and presence of ventricular or lumbar shunt [190].

High blood pressure is another factor considered to be related to a higher risk of bleeding [191]. Keeping systolic blood pressure under 160 mmHg seems to reduce the risk of re-bleeding. This value is considered to be reasonably safe in order to avoid delayed cerebral ischemia [192].

The current medical therapy for preventing bleeding is aimed at controlling blood pressure and preventing endogenous fibrinolysis.

- Maintain systolic BP below 160 mmHg (mean arterial pressure below 110 mmHg) [191]. There is no evidence about what type of drugs is to be used.
- Evaluate the intravenous infusion of tranexamic acid (1 g bolus, continuous infusion 1 g in 8 h) until endovascular or surgical procedure for exclusion of the aneurysm, up to a maximum of 24 h. Do not administer this therapy to patients with WFNS 1–2 without loss of consciousness at the time of bleeding, patients treated for deep vein thrombosis or pulmonary embolism, pregnant patients and patients with a history of renal or hepatic impairment [188]. In our centre, a subarachnoid hemorrhage is considered a medical emergency; therefore the aneurysm is secured as soon as possible and in any case within 24 h from the subarachnoid hemorrhage [193].

Delayed Cerebral Ischemia (DCI)

The most important complication for incidence and effect on prognosis is delayed cerebral ischemia (DCI), which occurs in 20–30 % of patients. Clinical deterioration caused by DCI is defined as the appearance of a focal neurological deficit (such as hemiparesis, aphasia, hemianopia or neglect) or deterioration by at least two points on the Glasgow Coma Scale (GCS), either in the total score or in each of its parts (eyes, verbal, motor on each side).

This deficiency must last at least 1 h; it must not be present immediately after the closure of the aneurysm and must not be attributable to other causes [194]. It is therefore a diagnosis of exclusion; in particular cerebral oedema, hydrocephalus, seizures, fever, metabolic disorders and drug effects must be excluded.

DCI may be associated with cerebral infarction, defined as a lesion detectable on a brain CT scan or MRI within 6 weeks from SAH, on the last brain CT scan or MRI performed within 6 weeks before the death of the patient or as a lesion at autopsy. This lesion should not be present on the CT scan or MRI performed between 24 and 48 h after closure of the aneurysm [194]. DCI occurs in 20–30 % of SAH patients and is identified as the main single factor for worse prognosis [111, 195]. DCI may occur but the neurological deterioration may not be recognized due to the poor clinical condition of the patient and/or administration of sedatives. Furthermore, cerebral infarctions may be detected on imaging but with no associated clinical manifestations [196]. A complex and multifactorial aetiology, which has not been fully identified, is recognized [197]. The following factors are involved:

Cerebral Vasospasm

This is defined as the narrowing of the lumen of the cerebral arteries following SAH. It has a typical time of onset and a typical development. It generally starts around day 5 with postbleeding and reaches a peak between day 5 and day 14 [198]. Pre-existing medical conditions associated with the development of vasospasm are hypertension and smoking [199].

The main factor related to the onset of vasospasm is the presence of subarachnoid clots detected by a scan [200, 201]. It is related to the assessment of a cerebral CT scan according to the Fisher scale [158]. Particularly significant for the onset of DCI is the presence of blood in the cisterns and in both lateral ventricles [202].

The pathophysiology of vasospasm is initially associated with the effect of oxyhaemoglobin on the muscular wall of

cerebral vessels, which induces an inflammatory cascade with smooth muscle contraction and consequent narrowing of the vessel lumen. This initial process is dependent on the entry of calcium ions into smooth muscle [203].

Endothelial wall damage may later develop, sustained by an inflammatory status associated with a decrease in the local availability of NO (vasodilator) [204] and increased synthesis of endothelin-1 (vasoconstrictor) [205]. Angiography of cerebral vessels is the gold standard for diagnosis [206].

Alternative techniques with good specificity and excellent diagnostic sensitivity are CT angiography and perfusion CT [207]. This latter technique does not evaluate the narrowing of the vessel lumen but evaluates cerebral perfusion; it should therefore be considered a diagnostic tool for DCI rather than vasospasm [208].

Vasospasm of cerebral vessels has historically been the single factor related to delayed neurological deterioration. However, the most recent research has instead revealed that there is close correlation between angiographically diagnosed vasospasm and DCI [209].

Early Brain Injury (EBI)

It occurs within 72 hours after SAH, and, it is related to the events immediately following the bleed. Bleeding in the subarachnoid space, with or without associated acute obstructive hydrocephalus, can cause acutely increased ICP above systolic pressure, with temporary arrest of cerebral flow. This phenomenon is responsible for the transient loss of consciousness present at the time of bleeding [210].

A transient cerebral ischemia occurs as a consequence of the sudden reduction of cerebral blood flow (CBF); various phenomena which are potentially related to onset of DCI have been described after transient cerebral ischemia: local inflammatory cascade, systemic inflammatory response, apoptosis, endothelial dysfunction and oxidative stress [211–214]. The relative contribution of each of these phenomena on the actual onset of the final DCI is not known.

Cortical Spreading Depolarization (SD)

SD is characterized by waves of depolarization which may be accompanied by waves of depression of cortical electrical activity. It has been proven that this phenomenon is present in patients with subarachnoid hemorrhage [215].

It is accompanied by alterations of electrolytes, which can cause an increase in metabolic demand and changes in the regional cerebral blood flow [216].

The presence of SD is associated with DCI regardless of the presence of vasospasm [217].

DCI Monitoring

It is necessary to establish early medical/instrumental treatment and to prevent the onset of cerebral infarction. The period of greatest risk for DCI onset is between day 3 and day 14 after the bleed. During this time of high risk, patients must be intensively monitored in an environment with multidisciplinary expertise, where there is an instrumental monitoring strategy and the multiple monitoring techniques can be interpreted so that an aggressive medical/interventional therapy can be delivered [218, 219].

Clinical Monitoring

Frequent neurological assessments are the basis of this clinical monitoring. Possible contributory causes of new neurological deficit must always be taken into consideration and ruled out (hydrocephalus, electrolyte disorders, infections, fever, hypoxia, seizures, NCSE). New episodes of DCI may present clinically with both a focal deficit with confusion, disorientation and stupor with often fluctuating trend. The sensitivity of clinical assessment in identifying DCI is greatly reduced if the patient is sedated or comatose (WFNS 4–5) [220].

Instrumental Monitoring

Baseline monitoring of patients at risk of DCI consists of transcranial Doppler [221]. It is carried out at least one to two

times in 24 h. It is a tool for evaluating the velocity of blood flow in brain vessels. To this purpose, the velocity of flow in the middle cerebral artery is monitored. Doppler of the middle cerebral artery has high specificity but low sensitivity [222, 223] for the presence of vasospasm; therefore it cannot be considered a diagnostic tool.

Monitoring of Delayed Cerebral Ischemia

Vasospasm must be monitored by transcranial Doppler in order to evaluate MCA flow velocity and the Lindegaard index. If blood flow velocity accelerates (MFVMCA 120–200 cm/s) and the Lindegaard index is between three and six, intense clinical monitoring must be continued and any hypovolaemia corrected. If the flow velocity accelerates by >200 cm/s and the Lindegaard index is >6, neuroradiological investigations must be carried out in order to treat the vasospasm.

Average velocimetry >160 cm/s with Lindegaard ratio >3 in the absence of fever and with normal arterial pCO2 (35–45 mmHg) [224, 225] are trigger criteria for carrying out more specific radiologic examinations (i.e. CT angiography or angiography).

Other instrumental monitoring procedures can be used for patients who are not clinically evaluable: local monitoring of local cerebral oxygenation (PtiO2), cerebral microdialysis and continuous EEG monitoring [226].

Medical Therapy

Several drugs have been tested in multiple studies in an effort to improve outcomes for SAH patients. Only oral administration of nimodipine appears to affect the outcome, and the administration of 60 mg of nimodipine every 4 h for 21 days post SAH is currently recommended [227, 228].

Intravenous administration of magnesium tested in the MASH-2 study does not reduce adverse outcomes compared with placebo in patients with aneurysmal SAH (RR 0.96, 95 % CI 0.84–1.10) [229].

Neuroprotective drugs such as tirilazad associated with nimodipine are not effective in improving the prognosis even though they reduce the risk of delayed cerebral ischemia (OR 0.80, 95 % CI 0.69–0.93) [230].

It has been suggested that cholesterol-lowering drugs can improve the prognosis of patients with aneurysmal SAH by improving endothelial function and increasing cerebral blood flow [231–233], thus preventing or reversing vasospasm. The recently published STASH study, which included 803 patients, showed no benefit in terms of prognosis at 6 months deriving from administering 40 mg of simvastatin daily for 21 days (primary ordinal analysis of the mRS, adjusted for age and WFNS on admission, OR 0.97, 95 % CI 0.75–1.25; $p = 0.803$) [234].

Medical therapy aims at preventing hypovolaemia and at increasing systemic arterial pressure in an attempt to maintain an adequate cerebral perfusion pressure. In addition to monitoring the water balance, an invasive monitoring of cardiac output and volume status of the patient is indicated in patients with more severe SAH [235].

An increase in cardiac output seems to be associated with increased cerebral blood flow, irrespective of blood pressure [236]. Induced hypervolaemia has no benefits on outcomes; [237, 238] it seems rather to be associated with an increase in complications [239].

The Cochrane meta-analysis evaluated the use of therapies aimed at increasing the circulating blood volume. Therapies such as human albumin 5 %, high-sodium crystalloid, colloids, plasma, whole blood or any combination of these did not demonstrate any improvement in prognosis (RR 1.0; 95 % CI 0.5–2.2) nor any reduction in the risk of delayed cerebral ischaemia (RR 1.1; 95 % CI 0.5–2.2); on the contrary there was a non-significant increase in the risk of complications (pulmonary oedema, heart failure (HF)) (RR 1.8; 95 % CI 0.9–3.7) [187].

In literature there are no recognised blood pressure target values. Arterial hypertension is obtained by infusion of nor-

adrenaline or dopamine. An increased cardiac output is obtained by infusion of dobutamine.

Endovascular Treatment of Vasospasm Resulting from Subarachnoid Hemorrhage

One of the most dramatic consequences of an SAH is the possible occurrence of vasospasm, usually in the period from 4 to 14 days after the bleeding episode. As previously described, vasospasm, which significantly reduces the calibre of the cerebral arteries, can lead to ischemia and infarction of wide areas, causing serious neurological clinical consequences and even death.

Over the last 30 years, the endovascular techniques that are used to cope with vasospasm have remained more or less unchanged, with no significant technological advancements and no important increases in the level of clinical success.

Substantially, two basic techniques have been used since the very beginning: injection of vasodilator drugs (medication) and angioplasty (mechanical treatment) carried out by inflating intravascular balloons.

Drug treatment began in the late 1980s with the use of papaverine, which was later replaced by nimodipine, when and where it became available (the injectable form of nimodipine is not available in the USA). These drugs should be injected into the arteries affected, but not necessarily in superselective areas: it may remain in the cervical segment of internal carotid or vertebral arteries. The drug is injected in a highly diluted form and very slowly (e.g. 4 mg of nimodipine diluted in 20–30 ml of saline injected in 10–20 min). The practice is still very operator-dependent and therefore varies from centre to centre. Papaverine must be diluted even more because it may form microcrystals.

The effectiveness of the pharmacological treatment is often valid, but unfortunately it is also often only transitory and so must be repeated. In some rare cases, continuous

treatment has been carried out for long periods of time (days), leaving a micro-indwelling catheter in the intracranial area.

The *mechanical treatment* (balloon angioplasty) seems to be more effective in maintaining its effect of arterial dilation over time. It is a more aggressive and potentially traumatic procedure, which must be done with great care by skilled personnel. Breaking the artery during dilation is obviously the main risk.

The balloons are those that are commonly used in cerebral procedures for vessel occlusion or to assist coil release in aneurysms ("balloon-assisted coiling"). Dilation must be carried out extremely gently at low volume and low pressure (the pressures used for expanding atherosclerotic plaques are absolutely not necessary for expanding vasospasm: normally one atmosphere is more than enough) while moving back and forth in the stretched spastic vessel.

The result is immediate. The main limitation of this technique is that it cannot be carried out in vessels of small calibre because of the risk of rupture that it carries. The internal carotid arteries, vertebral arteries and basilar arteries, but also the horizontal initial portion of the cerebral arteries, can be dilated. Balloon dilation of the start of the anterior or posterior cerebral arteries is not recommended, and the procedure must absolutely be avoided on more distal vessels.

Endovascular treatment of vasospasm often benefits from the combination of both techniques: the injection of drugs (nimodipine) to expand the entire vascular tree, even in its smallest and more distant branches, and dilation by angioplasty of larger and more proximal vessels.

It is clear that such treatment may be proposed only after trying all the available solutions in the field of neurological intensive care.

Endovascular treatment of vasospasm in asymptomatic patients as a prophylaxis of delayed cerebral ischemia does not improve the prognosis and is associated with the risk of fatal rupture of the artery [240].

Other Complications of SAH

Seizures

The incidence of seizures in patients with subarachnoid hemorrhage is about 15 %, with 7 % of seizures at onset [241]. They are often the manifestation of re-bleeding in the period when the aneurysm has not yet been secured.

Retrospective studies have identified several risk factors for seizures such as surgical clipping [242], severity of the initial neurological picture, blood clot density associated with subarachnoid blood, presence of intraparenchymal or subdural hematoma [241–244], associated ischemic events, cocaine abuse [245] and middle cerebral artery aneurysm. The incidence of epilepsy in the long term is 3–12 % [241, 246]. Although it is assumed that the occurrence of early seizures can cause additional damage, the independent effect of seizures on prognosis is not certain [122, 243].

A single large prospective study [247] has shown that the administration of phenytoin is independently associated with worse cognitive outcome; adverse effects associated with the use of antiepileptic drugs were reported in 23 % of the cases in another study [241]. There is no scientific evidence for prophylactic therapy [248]. In comatose patients with continuous EEG monitoring, a non-convulsive epileptic status was recorded in 10–20 % of the patients and this related to a worse outcome [249, 250]. It is independently associated with systemic inflammatory response syndrome (SIRS) after subarachnoid hemorrhage [251].

Fever

With any rise in temperature, infectious causes must be excluded. A central fever is most frequently of early onset (within 72 h of admission) and persistent [252]. Fever (defined as an internal temperature exceeding 38.3°C after subarachnoid hemorrhage) is a frequent complication, which affects between 30 and 70 % of the patients depending on the reported series. Fever is more frequent in patients with severe

subarachnoid hemorrhage [253–255], intraventricular hemorrhage [256] and vasospasm [257].

The presence of fever, often consensual to a non-specific inflammatory response (SIRS) [258], is associated with a worse outcome [111, 259, 260] in terms of disability and cognitive sequelae [253] and prolonged ICU stay [261].

The actual role of fever on prognosis is not clear; high brain temperature, however, is associated with increased cerebral metabolic stress [262] and with increased intracranial pressure [263]. It is also a factor that must be excluded in order to correctly evaluate new neurological deficits, in particular if a delayed cerebral ischemia is suspected.

Controlling central fever is therefore generally recommended, especially in the phases with an increased risk of vasospasm [264]. This can be obtained by administering antipyretics, through external cooling of the body surface by means of water-cooled cutaneous application plates or by means of intravascular catheters.

The administration of paracetamol or ibuprofen at scheduled times often does not allow optimal temperature control and is associated with hypotension [265]; continuous intravenous administration of NSAIDs is more effective [266]. The use of water-cooled plates or intravascular catheters seems to allow better temperature control [267], associated with a high incidence of shivering [268]. They are therefore reserved for already sedated patients with high-grade SAH [269].

Cardiovascular Complications

In subarachnoid hemorrhage patients, medical complications – in particular heart diseases – are directly responsible for 15–23 % of hospital mortality [254, 270]. Heart complications after subarachnoid hemorrhage might be due to an endogenous overactivation of the sympathetic system. Elevated levels of plasma norepinephrine were observed in patients for at least a week after bleeding [271]. A high level of catecholamines in the myocardium may cause toxic effects

on the cells, mediated by an increased influx of calcium [272]. In SAH patients, ECG changes can be observed as well as an increase in the enzymes of cardiac necrosis (troponins), markers of heart failure (BNP) and neurogenic stress cardiomyopathy (NSC).

- ECG changes are observed in variable percentages (25–75 %) [273]; more frequent abnormalities include ST elevation or depression, T-wave inversion, peaked T wave, and QT interval prolongation, which are associated with worse prognosis [274]. Arrhythmias include brady-/sinus tachycardia, atrial fibrillation/flutter, supraventricular tachycardia, premature ventricular junctional complexes rhythm and ventricular arrhythmias, which may play a role in causing sudden death after subarachnoid hemorrhage [275].
- An increased level of troponin in plasma is observed in 20–30 % of cases within 24 h of bleeding [110, 276, 277]; however, the increase is not as high as in patients with myocardial infarction [278]. In patients suffering from coronary artery disease, the possibility of a cardiac ischemia must be taken into consideration. An early BNP rise is observed in patients with left ventricular dysfunction [279].
- Neurogenic stress cardiomyopathy (NSC): This is characterized by early, transient left ventricular dysfunction. The degree of heart failure varies widely, from modest reduction in cardiac output to cardiogenic shock. Ventricular dysfunction is not due to a single area of coronary vascularization [280]; it partially shares the same features and pathophysiology as Takotsubo syndrome [281]. It is associated with the severity of the initial clinical picture [282] and independently related to an increased risk of delayed cerebral ischemia.

- Therefore, an ECG is recommended on admission, along with a dosage of troponin, for all SAH patients. Advanced monitoring of cardiac output and volume status of the patient is reasonable in patients with left ventricular

dysfunction documented by ultrasound [235]. Heart problems are often complicated by pulmonary oedema. Pulmonary oedema is treated with traditional therapy. Nitroglycerin as well as nitroprussiate must be avoided because of the vasodilator effect that raises intracranial pressure. For the same reason, hypercapnia should be avoided in the case of mechanical ventilation.

Hyponatraemia

Hyponatraemia (serum Na <135 mEq/L) is the most common electrolyte disorder and is present in 30–50 % of SAH patients [283]. The most frequent cause (70 %) is the syndrome of inappropriate antidiuretic hormone (SIADH), followed by fluid overload and acute deficit of cortisol [284, 285]. The association between hyponatraemia and worse outcome is not certain [259, 286].

Because of the potential risk of an increase in cerebral oedema, hyponatraemia is always treated even when it is very mild. The severity of the clinical picture influences treatment. Aggressive intervention with intravenous hypertonic infusion (1–3 ml/kg) is reserved for severe hyponatraemia (Na <130 mEq/l) with associated clinical manifestations (convulsions, depression of consciousness). In these cases the recommendation is a water balance every hour and monitoring of serum sodium every 4 h, in order to avoid hyperacute corrections and the known risks associated with them. Restricting water is the aetiological treatment of the syndrome of inappropriate secretion of antidiuretic hormone. It is not recommended in patients with subarachnoid hemorrhage associated with relative hypovolaemia [287].

The administration of hydrocortisone and fludrocortisone has been tested in controlled studies for the prevention of hyponatraemia. Both corticosteroids were effective, but with a higher incidence of hyperglycaemia and hypokalaemia [288–291].

1.3 Appendix

1.3.1 ICH Score [36]

Determination of ICH score	
Component	**ICH score points**
GCS score	
3–4	2
5–12	1
13–15	0
ICH volume, cm^3	
≥30	1
<30	0
IVH	
Yes	1
No	0
Infratentorial origin of ICH	
Yes	1
No	0
Age, y	
≥80	1
<80	0
Total ICH score	0–6

GCS: Glasgow Coma Scale; ICH: Intracerebral hemorrage; IVH: Intraventricular Hemorrhage.

1.3.2 Evaluation Scales

Hunt and Hess grading system [148]

1. Asymptomatic or mild headache and slight nuchal rigidity
2. Moderate to severe headache, nuchal rigidity, no focal neurologic deficit other than cranial nerve palsy
3. Confusion, lethargy or mild focal neurologic deficit other than cranial nerve palsy
4. Stupor or moderate to severe hemiparesis
5. Coma, extensor posturing, moribund appearance

World Federation of Neurological Surgeons (WFNS) grading scale and outcome [151]

Grade		Poor outcome (%)
Good		
I	GCS 15	14.8
II	GCS 14–13 without focal deficit	29.4
III	GCS 14–13 with focal deficit	52.6
Poor		
IV	GCS 12–7	58.3
V	GCS 6–3	92.7

Adapted from van Heuven et al. [156]
Poor outcome: GCS 1–3 or modified Rankin score 4–6
GCS Glasgow Coma Scale

Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage (PAASH) grading scale and outcome

Grade		Poor outcome (%)
I	GCS 15	14.8
II	GCS 11–14	41.3
III	GCS 8–10	74.4
IV	GCS 4–7	84.7
V	GCS 3	93.9

Adapted from van Heuven et al. [156]
Poor outcome: GCS 1–3 or modified Rankin score 4–6
GCS Glasgow Coma Scale

Radiological evaluation scale

Grade	Fisher scale	modified Fisher scale
0	—	No subarachnoid or intraventricular hemorrhage
1	No subarachnoid hemorrhage or intraventricular hemorrhage	Minimum or thin subarachnoid hemorrhage, no intraventricular hemorrhage in either lateral ventricle
2	Diffuse, thin subarachnoid hemorrhage, no clot >1 mm in thickness	Minimum or thin subarachnoid hemorrhage, with intraventricular hemorrhage in both lateral ventricles
3	Localized thick layer of subarachnoid clot >1 mm in thickness	Thick subarachnoid hemorrhage, no intraventricular hemorrhage
4	Predominant intraventricular hemorrhage or intracerebral hemorrhage without thick subarachnoid hemorrhage	Thick subarachnoid hemorrhage with intraventricular hemorrhage in both lateral ventricles

Risk of vasospasm: 0% for grade 0; 6% for grade 1; 15% for grade 2; 35% for grade 3; 34% for grade 4 [158, 159]

PHASES ANEURYSM RISK SCORE [100]

(P) Population	
North American, European (other than Finnish)	0
Japanese	3
Finnish	5
(H) Hypertension	
No	0
Yes	1
(A) Age	
<70 years	0
>= 70 years	1
(S) Size of aneurysm	
<7.0 mm	0
7.0–9.9 mm	3
19.0–19.9 mm	6
>0 20 mm	10
(E) Earlier SAH from another aneurysm	
No	0
Yes	1
(S) Site of aneurysm	
ICA	0
MCA	2
ACA, PCom, posterior	4

Glasgow Coma Scale (GCS)

Eye opening		Verbal response		Motor response	
Opens spontaneously	4	Normal conversation	5	Normal	6
Opens to voice	3	Disoriented conversation	4	Localizes pain	5
Opens to pain	2	Words incoherent	3	Withdraws from pain	4
None	1	Incomprehensible sounds	2	Decorticate posturing	3
		None	1	Decerebrate posturing	2
				None	1

Cognard classification [69]

The Cognard classification correlates venous drainage patterns with increasingly aggressive

Type I

Confined to sinus wall, typically after thrombosis

Type II

IIa – confined to sinus with reflux (retrograde) into sinus but not cortical veins. Into sinus with reflux (retrograde) into cortical veins (10–20 % hemorrhage) IIb – drains

Type III

Drains direct into cortical veins (not into sinus) drainage (40 % hemorrhage)

Type IV

Drains direct into cortical veins (not into sinus) drainage with venous ectasia (65 % hemorrhage)

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Chapter 2
Clinical Cases

Elio Agostoni, Edoardo Boccardi, Marco Cenzato, and Marco Longoni

In this chapter a series of clinical cases explanatory of the various conditions relating to the pathology are collected and presented.

2.1 Case Study No. 1

A 49-year-old Asian female presented to the emergency department after the sudden onset of left-side hemiplegia. Her past medical history revealed high blood pressure and scarce compliance to therapy, as well as a previous cerebellar hemorrhage in the right hemisphere 3 years before the ongoing event. Angiography had given negative results for arteriovenous malformations (AVM) but had shown evidence of a diffuse vasculopathy in the main arterial branches in the circle of Willis. On arrival at the emergency department, the neurological clinical examination found a right-side hemiplegia.

The brain CT scan carried out in urgency found hemorrhaging of the left basal nuclei. The patient was therefore given an emergency CT angiography (see Fig. 2.1A–C).

The CT angiography (Fig. 2.1D, F, G) found no evidence of arteriovenous malformations near the hemorrhage, but it did confirm various diffuse alterations in the size of the intracranial arteries (red arrows), corresponding perfectly to the

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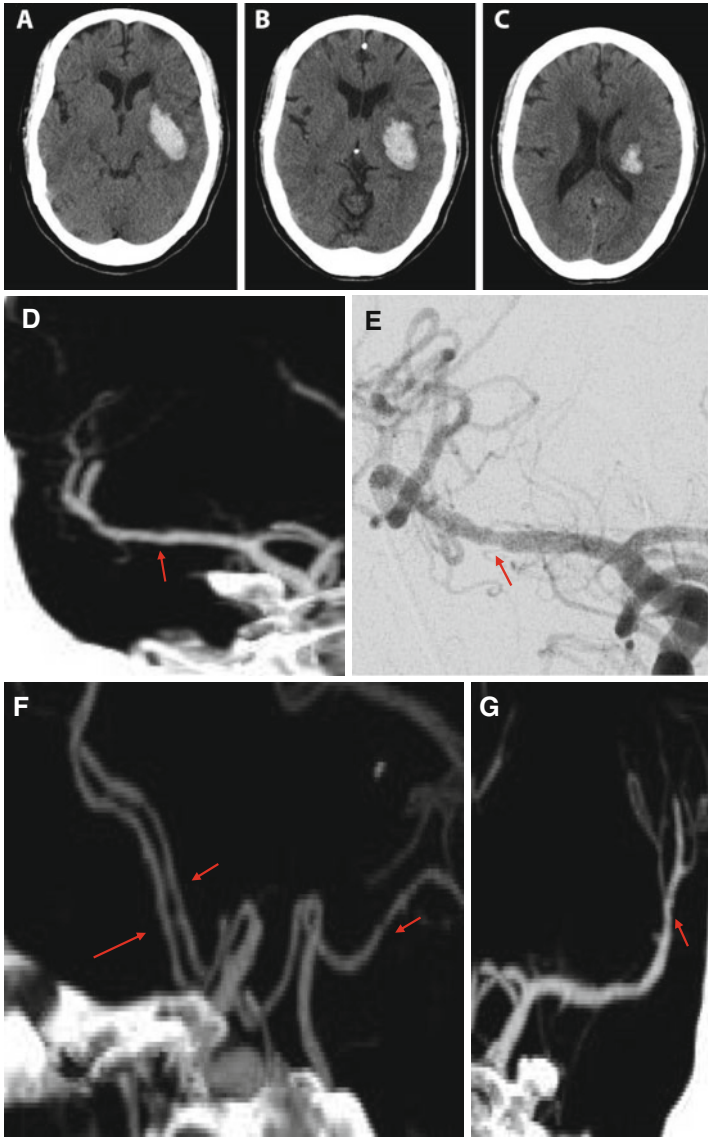


Figure 2.1

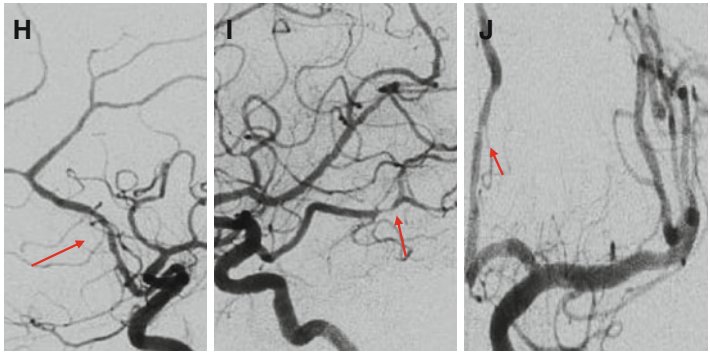


FIGURE 2.1 (continued)

angiography investigations carried out during the previous hospital admittance (Fig. 2.1E, H–J). The patient was admitted to the stroke unit in order to monitor her vital signs. On arrival at the unit, the neurological examination showed patient's eyes were open, total language barrier, right-side hemiplegia with spastic hypertonia, and movement of the left limbs retained (NIHSS 17/42).

During the patient's hospitalization, antihypertensive therapy was increased with erratic checking of diastolic pressure.

Five days after admittance, a state of sopor appeared with a Glasgow Coma Scale score of 6/15. An urgent brain CT scan was carried out (Fig. 2.2).

The brain CT scan showed an extensive right-side cerebellar bleeding site with mass effect on the adjacent structures and obliteration of the fourth ventricle.

A neurosurgeon was urgently contacted and prepared for surgical evacuation of the hematoma and posterior fossa decompression.

The postoperative CT (Fig. 2.3) showed that the cerebellar hematoma had been completely removed, with a marked reduction in the mass effect and a possible view of the fourth ventricle. Finally, pneumocephalus was noted. The patient was then transferred to intensive therapy, and a right-side frontal external ventricular shunt was put into place. Finally

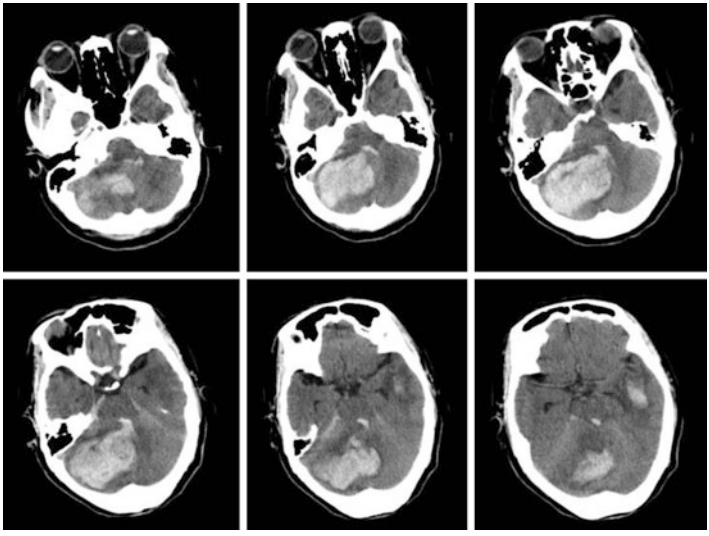


Figure 2.2

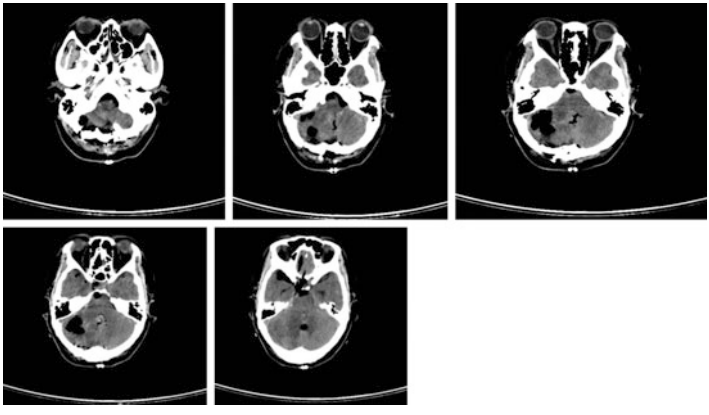


Figure 2.3

a tracheostomy was setup. Progressive clinical improvement was then observed. The patient was returned to the stroke unit 7 days after surgery with the neurological examinations

reported as follows: patient alert, language barrier, unable to carry out commands, right-side hemiplegia, and valid response to pain stimulus on the left side.

After 25 days of hospitalization, the patient was sent to rehabilitation for serious cerebral lesions with mRS 5/6.

Discussion

In this case the occurrence of an infratentorial bleeding together with a severe neurological deterioration is the key indicator for surgical decision. From STICH trial we know that in these cases the surgical approach is linked with a higher likelihood of a better outcome [1].

2.2 Case Study No. 2

Hemorrhage in a patient under anticoagulant therapy (warfarin).

A 70-year-old white Caucasian male was brought to our attention with a medical history of hypertension, type 2 diabetes mellitus with associated retinopathy, previous retinal thrombosis in the right eye, two previous episodes of brain hemorrhages in the basal nuclei which had occurred approximately 5 years before the present hospital admittance with no residual disability, recent replacement of the aortic valve with a bioprosthesis, and mitral annuloplasty. He was undergoing antiplatelet therapy at home (100 mg acetylsalicylic acid), oral anticoagulant (warfarin sodium according to INR), antihypertensives (ace inhibitors and beta-blockers), statins, and oral hypoglycemic agents.

On the day he was admitted, there was a sudden appearance of global aphasia and repeated vomiting.

INR in the emergency department: 1.86.

On arrival in the ER, the patient was given an urgent brain CT scan (Fig. 2.4).

The scan showed a large hemorrhage of the left basal nuclei breaking through into the ventricular system and mass effect on the lateral ventricle. In the ER the patient was

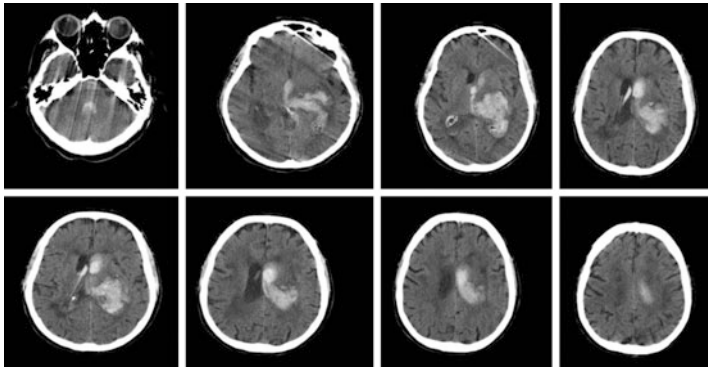


FIGURE 2.4

promptly recoagulated with a prothrombin complex (Prothromplex 2000 UI) with a final INR of 1.2. The neurosurgeon assessed the patient and did not find indications for treatment, considering the patient's age and the location of the hemorrhagic lesion. The neurological assessment is as follows: patient in a coma, eyes closed, anisocoria left > right photoreactive, torpid bilateral oculocephalic reflexes, reduced right corneal direct and consensual reflexes, decerebrate response to pain stimulus in both arms, slight flexion of both legs, bilateral Babinski, no meningeal signs, regular breathing, and occasional snoring. The patient was admitted to the stroke unit in a serious clinical condition followed by further clinical deterioration.

GCS = 3 after 24 h. Deceased after 48 h.

2.3 Case Study No. 3

We present the case of a 50-year-old male of African race whose medical history reveals no significant pathologies. The patient presented to the ER after approximately 3 days of serious persistent headache. It must be pointed out that the headache appeared suddenly, and the pain was described as severe and pulsating, associated with an episode of pro-

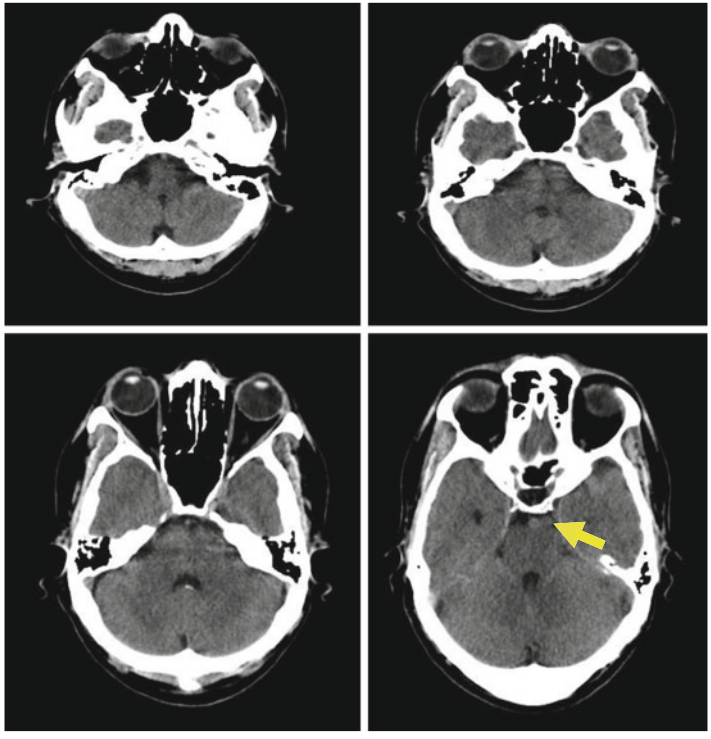


FIGURE 2.5

jectile vomiting. The clinical examination in the ER revealed no focal deficits. A brain CT scan was then carried out (Fig. 2.5).

The scan showed an iso-hyperdense parapontine formation compatible with a clot (Fig. 2.5, yellow arrow). As a subacute subarachnoid hemorrhage was suspected, an urgent CT angiogram was carried out, which showed no aneurysmal lesions; a lumbar puncture was then performed. The results of fluid tests showed that proteins and CSF are within the norm and spinal fluid is yellow. Diagnosis of a non-aneurysmal SAH was confirmed. The patient was then hospitalized in a stroke unit, and an angiogram was carried out, with results

within the norm (data not displayed). The clinical course was regular and the patient remained asymptomatic. He was discharged after 5 days under observation with indications for a follow-up angio-MR scan and a brain MR scan approximately 1 month after the episode.

Discussion

In non-aneurysmal subarachnoid hemorrhage, the opportunity of a repeated conventional angiography examination is debated. From literature we know that repeat angiography seems to be justified only when the initial examination is technically inadequate, when vasospasm is present, or if further bleeding occurs [2].

2.4 Case Study No. 4

(Amyloid angiopathy)

We present the case of an 80-year-old Caucasian female who presented at ER following the sudden onset of right-side hemiplegia. The medical history documented chronic obstructive bronchopneumopathy and osteoporosis. The patient was not taking antiplatelet or anticoagulant therapies. The clinical neurological examination in the ER showed an NIHSS of 8/42 due to asthenic deficit in the right-side limbs.

An urgent brain CT scan was performed (Fig. 2.6).

The brain CT scan showed evidence of a hemorrhagic lesion in the left frontal cortico-subcortical parietal region with minimal bleeding into the adjacent, smoothed, cortical sulci and a modest imprint on the posterior portion of the middle ventricular cell, as well as a clearly hypodense area in the right temporal cortico-subcortical region, with a modest ex-vacuo enlargement of the temporal horn. Taking into consideration the characteristics of the hemorrhage, further investigation was carried out by means of an urgent diagnostic Angio-CT scan (Fig. 2.7).

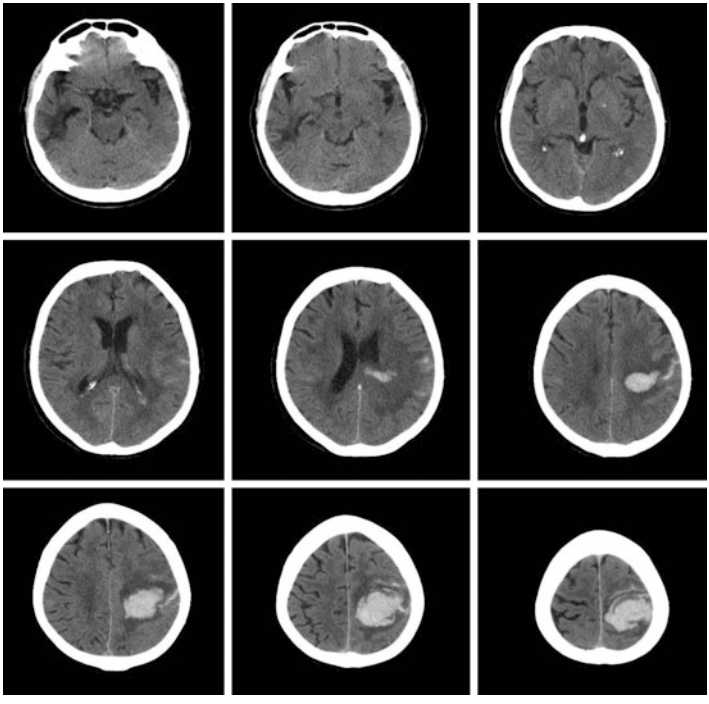


Figure 2.6

The Angio-CT scan did not show any arteriovenous malformations or arteriovenous fistulas. Finally, the patient was assessed by the neurosurgeon who reached the conclusion that treatment to evacuate the hematoma was not indicated due to the patient's age and clinical condition. The patient was admitted to a stroke unit for continuous monitoring. She was discharged on day 14 to a rehabilitation center with mRS = 4 and BI 10/100. A brain MR scan was recommended approximately 2 months after hospitalization. Five months after discharge, the patient was brought to the ER due to the onset of a motor deficit in the left-side limbs in association with nausea, vomiting, and a slightly raised temperature.The

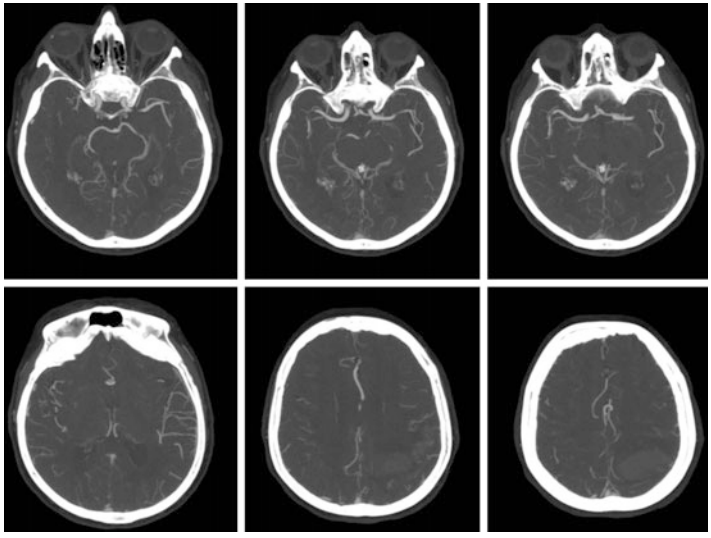


Figure 2.7

clinical examination in the ER revealed that the patient was soporous and scarcely collaborative, with persistent right-side hemiplegia (as outcome) and slight left-side hemiparesis (NIHSS = 30/42). An urgent brain CT scan was carried out (Fig. 2.8).

The brain CT scan revealed the site of an intraparenchymal bleed (max. size approx. 5.6 × 4.2 cm on the axial plane) in the frontobasal and right frontopolar regions, surrounded by a moderate amount of perilesional edema, causing a discrete mass effect on the homolateral frontal horn, with minimum contralateral shift of the median structures. The patient was admitted to a stroke unit; no indications were proposed for neurosurgical intervention. The patient was discharged after 14 days with mRS = 5 and transferred to a ward for serious cerebral lesions. On the basis of the patient's clinical and instrumental history, the conclusive diagnosis was amyloid angiopathy.

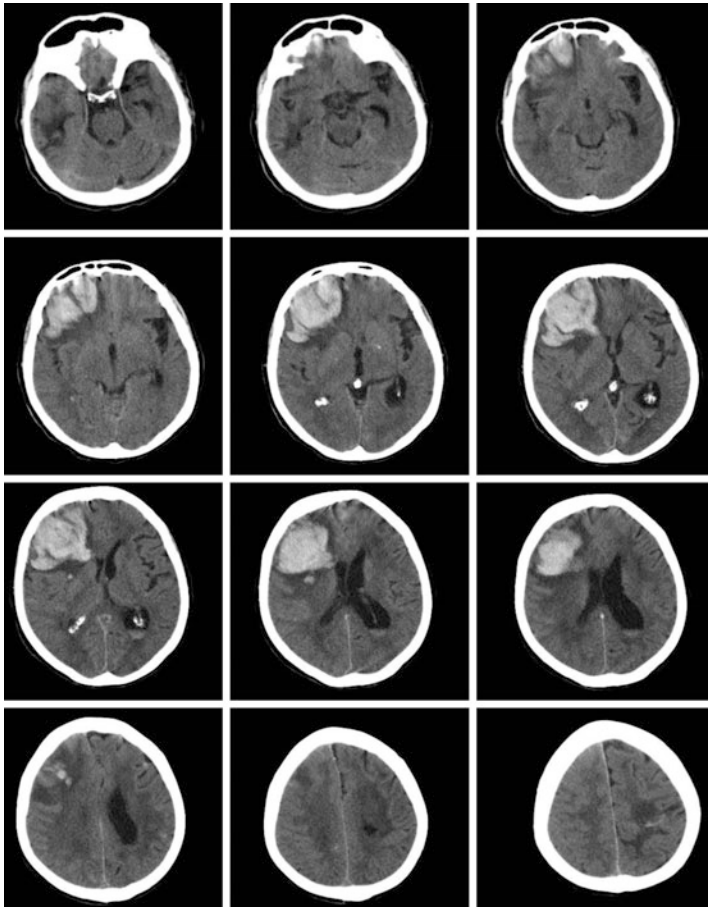


Figure 2.8

2.5 Case Study No. 5

Sine materia SAH

A 74-year-old Caucasian male was brought to our attention. His medical history showed hypertension. He had been sent from another hospital because a brain CT had revealed

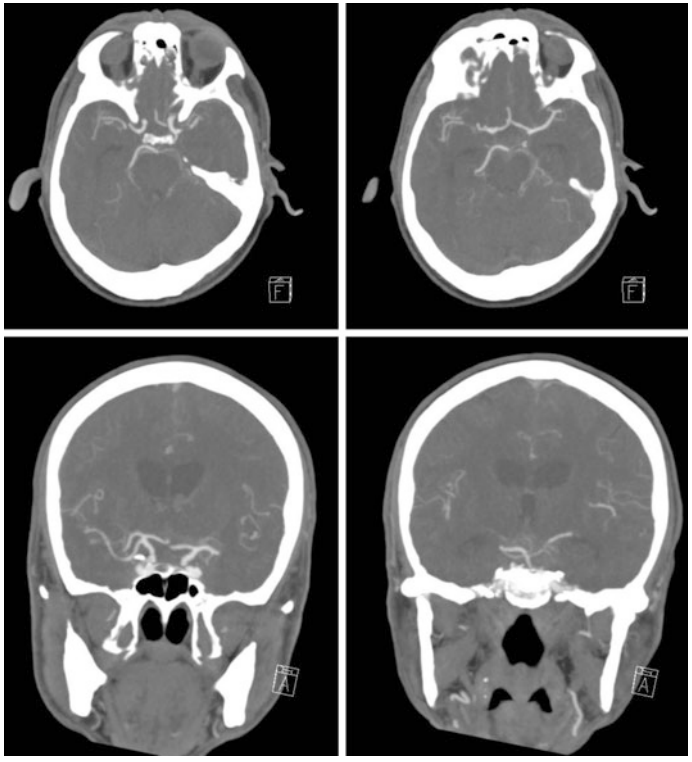


Figure 2.9

a subarachnoid hemorrhage. From a neurological point of view, the patient presented focal deficits with a GCS of 15/15. An urgent angio-CT scan was performed as well as an assessment of the brain CT scan (Figs. 2.9 and 2.10).

The brain CT scan confirmed the presence of a subarachnoid hemorrhage in the basal cisterns and sylvian fissures as well as some blood component in the III and IV ventricle with slight dilation of the ventricular cavities. The angio-CT scan did not show any imaging to suggest aneurysmal dilations. After hearing the opinion of the neurosurgeon, an angiogram was arranged (Fig. 2.11).

The angiogram confirmed the absence of aneurysmal dilations and cerebral arteriovenous malformations. The patient

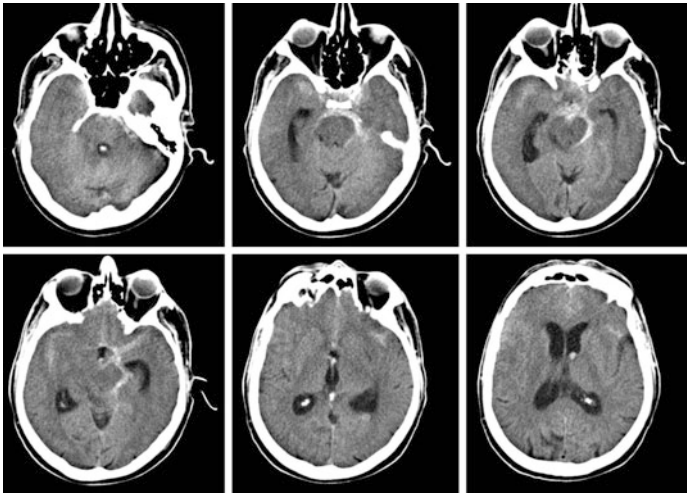


Figure 2.10

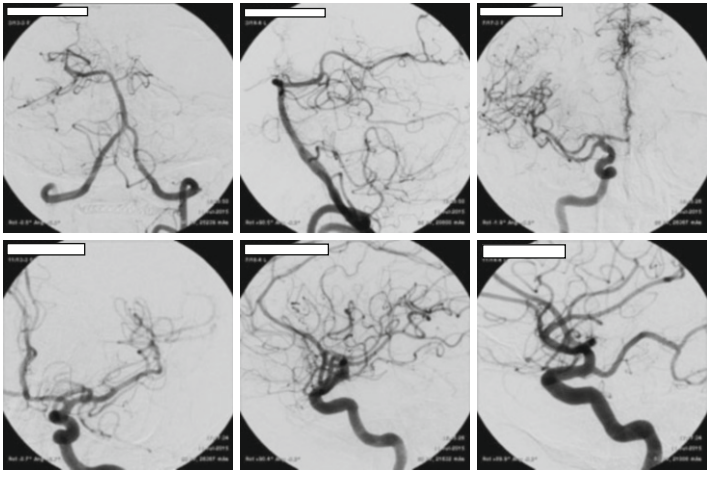


Figure 2.11

was admitted to the stroke unit for clinical-instrumental monitoring. The neurological clinical examination continued to be negative, with GCS = 15/15; nuchal headache persisted

(VAS 7/10) with good response to paracetamol. Considering the nature of the subarachnoid hemorrhage revealed in the first CT scans, the decision was made to repeat an angiographic exam approximately 2 weeks from onset of the clinical episode. The results of the second angiogram were also within the norm, thus excluding the presence of intracranial vascular alterations as the cause of the hemorrhage. The patient was discharged on day 20 without symptoms.

Discussion

As stated before, the repetition of an angiography in cases of non-aneurysmal SAH is usually unnecessary. In this case we decided to do it because of slight hydrocephalus on first CT scans and for the amount of blood that was not typical for a perimesencephalic SAH.

2.6 Case Study No. 6

We present the case of a 29-year-old Caucasian male with a substantially clear medical history. The patient was brought to our attention due to a nocturnal episode of loss of consciousness with morsus, sphincter incontinence, and successive neck pain. Assisted by the paramedics, he was initially found unconscious but regained consciousness after 10 min with no neurological deficits. The patient arrived in the ER department of our hospital, GCS 15, and underwent a brain CT scan (Fig 2.12) and an Angio-CT (Fig. 2.13).

The brain CT scan revealed a diffuse subarachnoid bleed in the basal cisterns, in peribulbar and parapontine areas, and in the sylvian fissures.

The CT angiogram showed up the presence of three aneurysmal formations, one of which in the left posterior inferior cerebellar artery (PICA) (Fig. 2.13 arrow head) and two alterations of the right carotid artery, respectively, in the supraclinoid tract (Fig. 2.13 black arrow) and at the apex of the carotid (Fig. 2.13 red arrow).

After discussing the case with the interventional neuroradiologists and neurosurgeons, indication was found for endo-

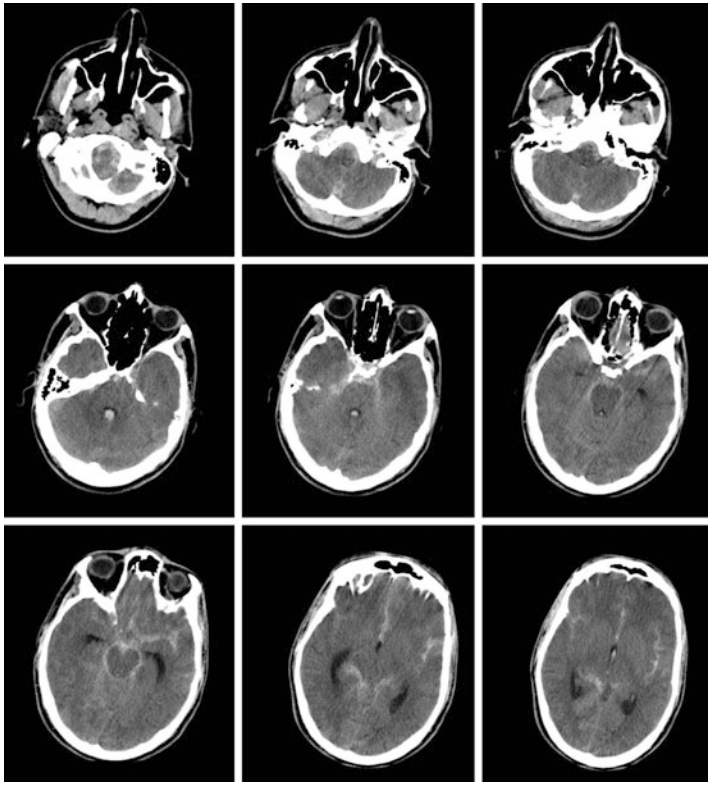


Figure 2.12

vascular treatment. As the cause of the subarachnoid bleed could not be determined with any certainty, closure of all the aneurysms was the treatment of choice.

Cerebral angiography was carried out under general anesthetic.

The angiogram confirmed the presence of a wide-neck aneurysmal dilation at the origin of the left PICA (Fig. 2.14A–C), an aneurysmal dilation of the origin of the right posterior communicating artery, and a further dilation at the internal right carotid terminus (Fig. 2.14F–I). Treatment was begun on the three aneurysms, starting with the aneurysm in the PICA (Fig. 2.14D, E) and then moving on to the right carotid with

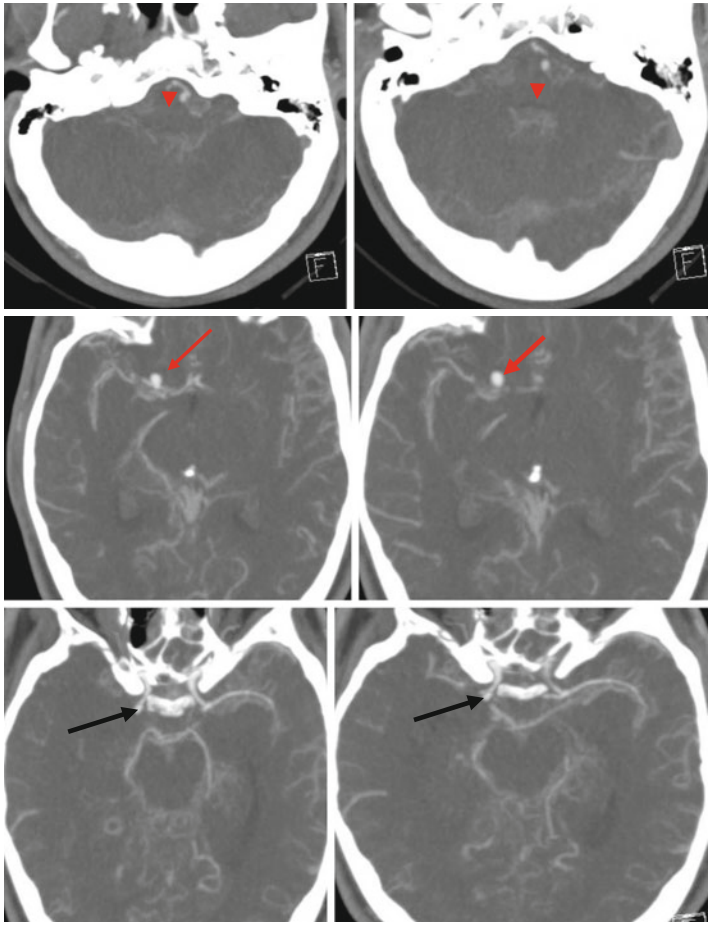


Figure 2.13

occlusion, before treating the more distal aneurysm (carotid terminus) (Fig. 2.14L, M). Finally the more proximal aneurysm was occluded (Fig. 2.14N, O) with platinum spirals (right posterior communicating artery). The final check showed that the aneurysms had been completely occluded with no occlusions of the parent vessels (Fig. 2.14D, E, P, Q).

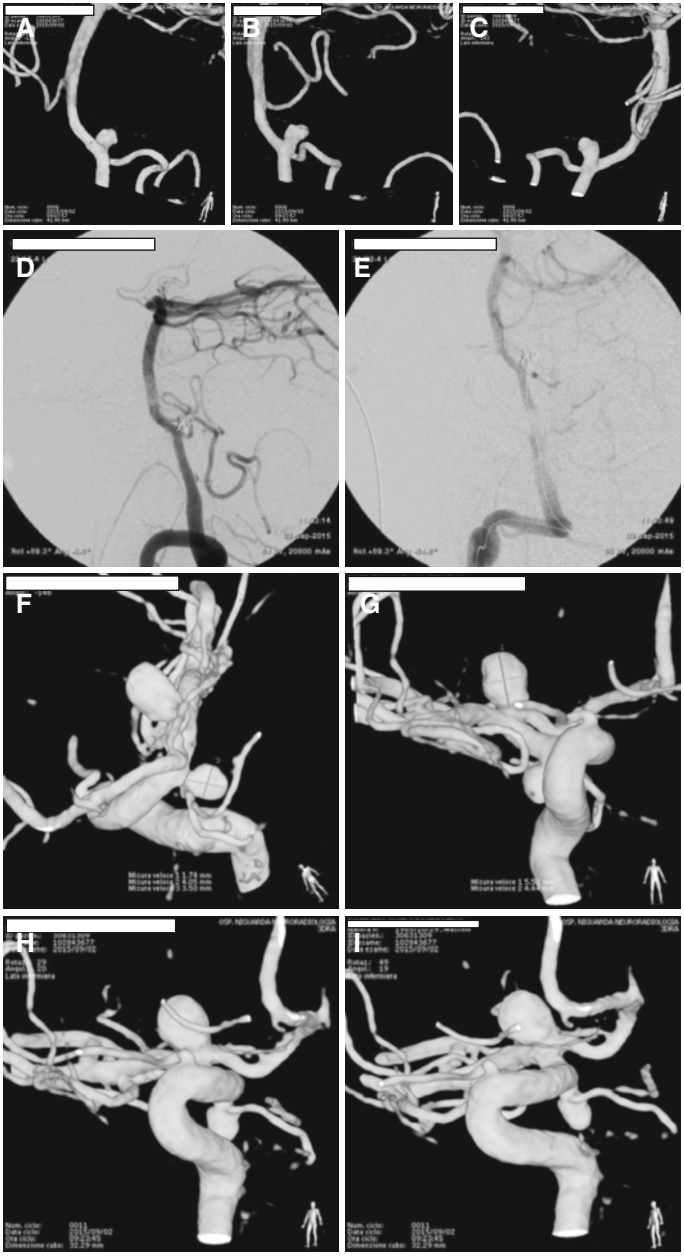


Figure 2.14

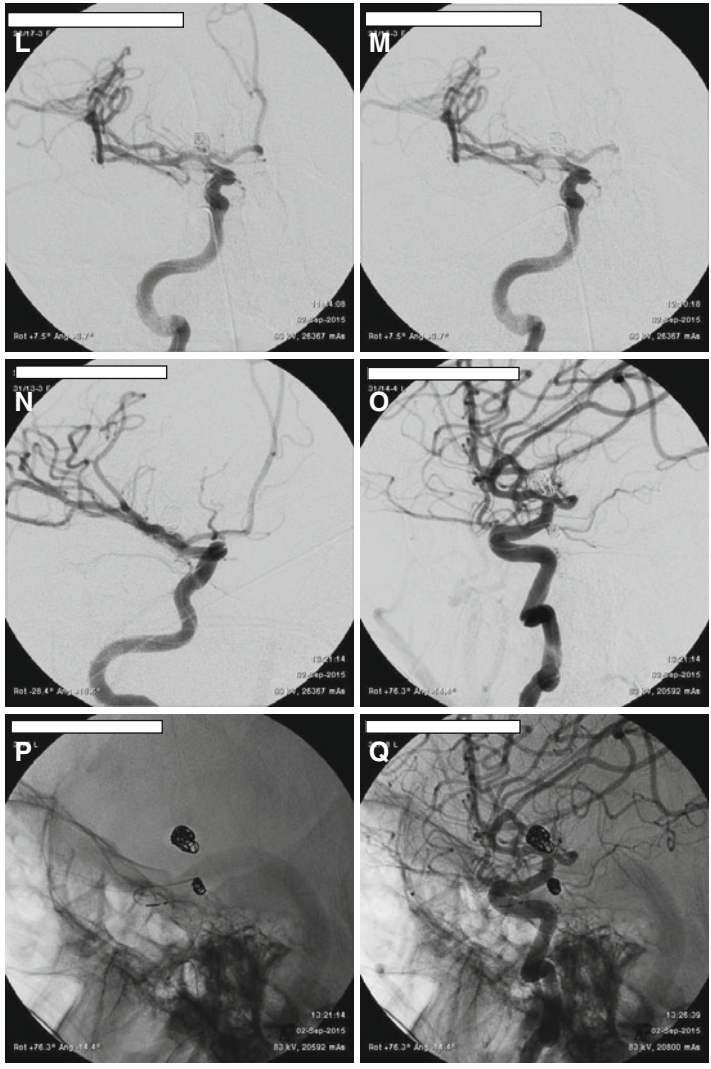


FIGURE 2.14 (continued)

The postoperative CT scan (Fig. 2.15) showed that the ventricles had increased in size; it was therefore decided to apply an external ventricular shunt. The patient was then admitted to the neurointensive care unit for ICP monitoring and a transcranial

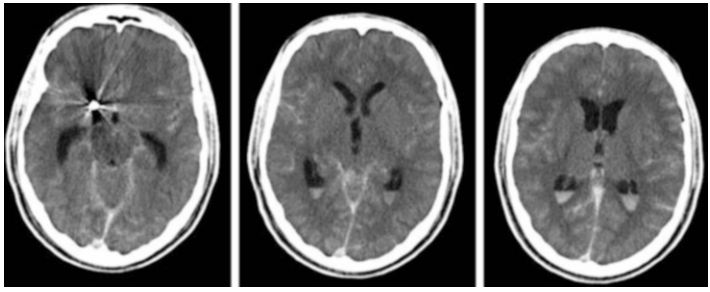


Figure 2.15

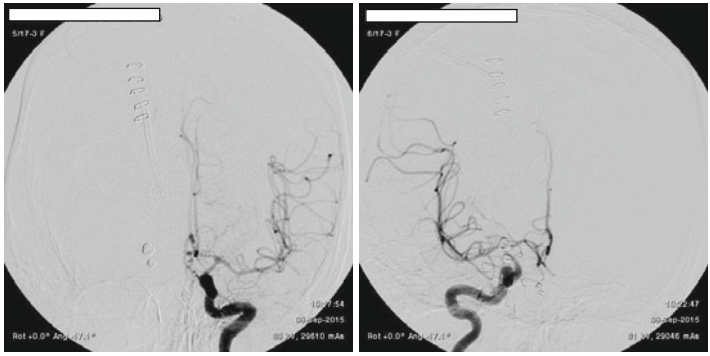


Figure 2.16

Doppler. He was prescribed oral therapy with nimodipine and crystalloid infusion to maintain a hypervolemic condition. After the transcranial Doppler revealed an initial increase in arterial velocity values in all the cerebral vessels, an intracranial CT angiogram (data not shown) was carried out, which confirmed the initial vasospasm indicated by the ultrasound. The decision was therefore taken to give the patient an angiography session (Fig. 2.16) to treat the vasospasm with intra-arterial nimodipine.

Successive instrumental monitoring revealed first of all some instability of the velocimetric values and then a successive reduction until the values returned to normal. From a clinical viewpoint, the patient's temperature rose, and he was in soporous without ever displaying focal deficits. On day 5 he was transferred from the neurointensive care unit to the

stroke unit. The neurological clinical examination was normal except for a stiff neck. The shunt was removed on day 13. The patient was discharged on day 27 in a clinically normal condition and mRS 1/6.

Discussion

The patient was referred to endovascular treatment instead of surgery because of aneurysms' location. From ISAT trial we know that endovascular treatment of ruptured aneurysm is safer and equally effective with respect to surgical clipping [3].

In patients with multiple aneurysms and the uncertainty of which of them was responsible for SAH, the decision to perform a simultaneous multiple coiling, as it was in our case, or clipping might be taken into consideration [4, 5].

2.7 Case Study No. 7

We present of a 45-year-old female of South American origins who arrived in the emergency room (ER) with sudden migraine and confusion. A neurological examination (NE) revealed rigor and nuchal headache; neurological assessment resulted normal with Glasgow Coma Scale (GCS) 15.

Her medical history showed anxiety, depression, and substance abuse (cocaine). An emergency computed tomography (CT) of the brain was performed on the patient (Fig. 2.17).

The brain CT scan showed the presence of cerebral hemorrhage in the cisterns of the lower section and of the sylvian fissures, primarily on the right side. Hunt and Hess Scale grade 2, Fisher scale 2.

The AngioCT scan (Fig. 2.18) revealed a saccular aneurysm located at the base of the right carotid artery (see arrows).

After collectively discussing the case, the decision was made to carry out endovascular treatment as an emergency procedure under general anesthesia.

The patient was given endovascular treatment (Figs. 2.19, 2.20 and 2.21) to embolize the aneurysm (Fig. 2.19a, b) with

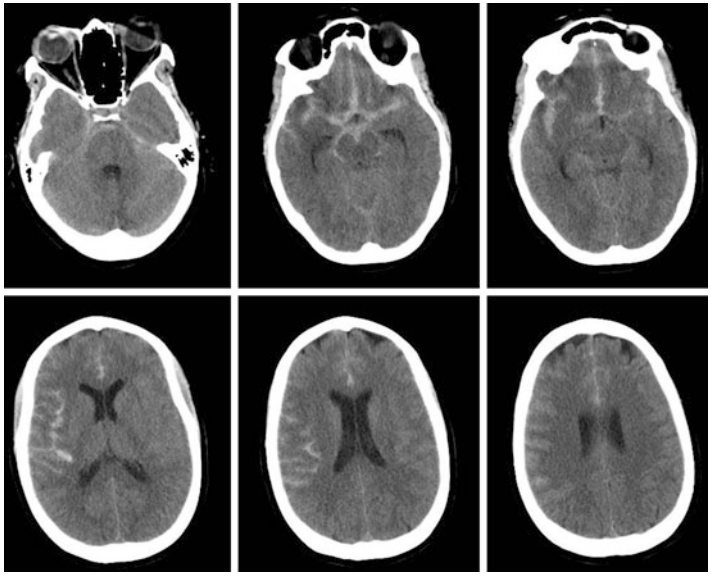


Figure 2.17

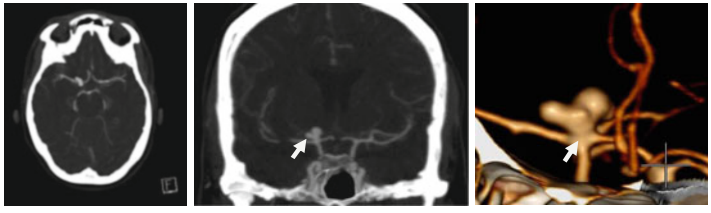


Figure 2.18

controlled detachable platinum coils (see arrow). Final examinations showed evidence that the aneurysm sac had been almost completely excluded from the intracranial blood flow (Figs. 2.20A, B and 2.21A). The patient was subsequently admitted to the intensive care unit (ICU) for postoperative monitoring. A therapy of oral nimodipine was prescribed to prevent vasospasm.

Pre treatment

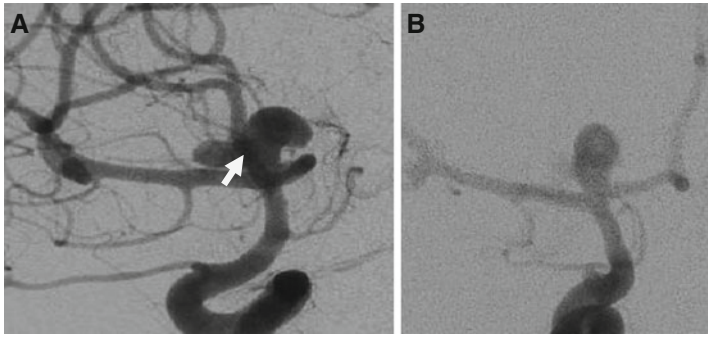


FIGURE 2.19

Post treatment

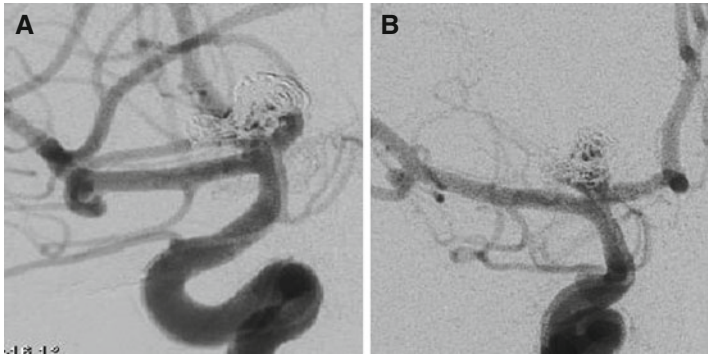


FIGURE 2.20

From a clinical point of view, the patient showed no significant deficits from day 1 to day 4 after surgery. The patient was then transferred to the stroke unit. On the 7th day after the subarachnoid hemorrhage (SAH) occurred, muscle weakness appeared in the left limbs and a transcranial Doppler (TDC) demonstrated a significant acceleration of blood-flow velocity in the middle cerebral artery (MCA), mainly on the right side, with a Lindegaard index of 5.6. A brain CT was performed which showed no evidence of early hypodense structures (not shown). CT angiogra-

Final check

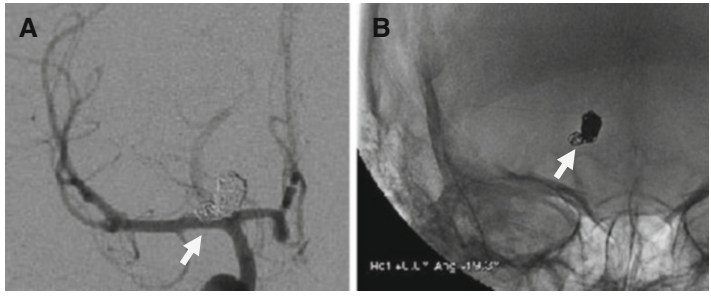
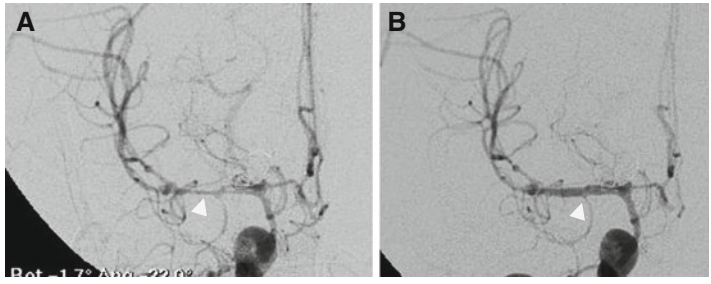


Figure 2.21



Pre-PTA Post-PTA

Figure 2.22

phy (CTA) was also performed, which revealed the presence of a diffuse cerebral vasospasm (data not shown), mainly involving the flow of the right carotid artery. The patient was admitted to the intensive care unit (ICU) and underwent sedation and hypothermia. Clinical conditions remained stable with persistent hemiparesis of the left limbs. For this reason cerebral angiography was performed to treat the vasospasm. An initial cerebral angiography (Fig. 2.22) was carried out with intra-arterial infusion of nimodipine. The following day the vasospasm was still diagnostically and clinically persistent; it was therefore decided to proceed with an angioplasty of the stenosis of the right middle cerebral artery (ACM) on the right-hand side (see top arrow) via ultrasoft percutaneous transluminal balloon angioplasty (PTA).

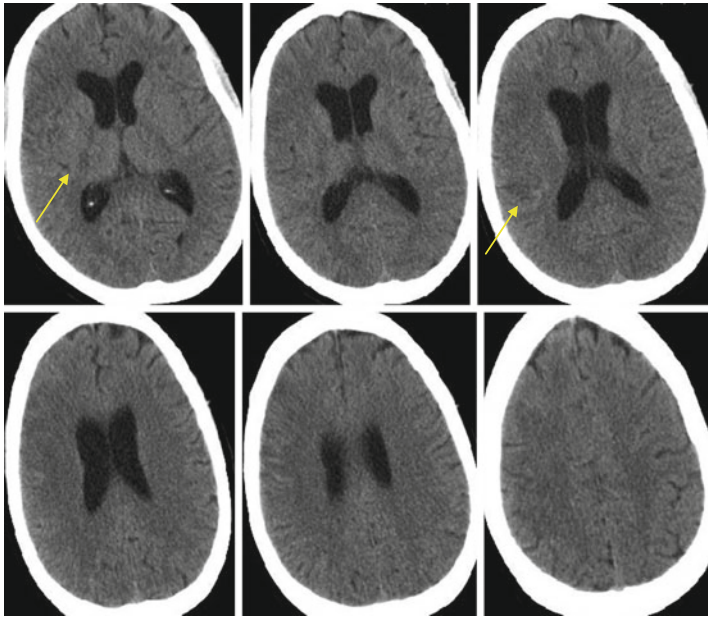


FIGURE 2.23

Pre-percutaneous transluminal angioplasty (PTA). Post-percutaneous transluminal angioplasty (PTA).

Angiographic images (Fig. 2.22B) showed a recovery of blood flow in the proximal portion of the middle cerebral artery (ACM) with the persistence of a significant distal vasospasm. Brain CT scan (data not shown) showed a deep hypodense lesion in the basal nuclei. From a clinical viewpoint, the patient showed gradual improvement of the muscle function of the left leg, while muscle weakness remained persistent in the arm, with spastic hypertonia. The diagnostic procedures showed gradual resolution of the vasospasm with a normal transcranial Doppler (TDC) 18 days after the subarachnoid hemorrhage (SAH). Calcium channel blocker (CCB) therapy was continued until day 21, with subadministration suspended thereafter. The patient underwent computed tomography (CT) before discharge (Fig. 2.23).

There were no new ischemic lesions and no signs of hydrocephalus. There was evidence of a lesion in the basal nuclei and right-side operculum. A magnetic resonance spectroscopy (MRS) was performed prior to discharge.

Discussion

In this case the occurrence of protracted and severe vasospasms might be explained together with the SAH also because of cocaine abuse as it is suggested by data from literature [6].

Regarding the best therapeutic approach of cerebral vasospasm, many are the data in literature with no conclusive reports. The use of oral nimodipine in a prophylactic manner is the only therapy based on EBM [7]. In our case we firstly treat the patient with the administration of nimodipine intra-arterially [8]. Because of clinical deterioration despite the intra-arterial therapy, we decided to move forward with a more invasive approach using angioplasty. Several case reports have supported this endovascular procedure [9]; however in our case despite angioplasty the patient developed a cerebral infarction.

2.8 Case Study No. 8

We present of a 72-year-old Caucasian female with a remote medical history of arterial hypertension, dyslipidemia, and hypothyroidism. The patient had been admitted to another hospital due to a sudden and severe state of confusion, and a brain CT (not shown) had revealed a hemorrhagic lesion and accompanying edema. An urgent magnetic resonance imaging (MRI) of the brain was performed (Fig. 2.24).

Magnetic resonance imaging (MRI) of the brain confirmed the presence of a bleeding site with an edema expanding into the surrounding area (star). On sequences after gadolinium injection the evidence of vascular serpiginous/ring structure alterations localized in the temporal and parietal region was depicted (Fig. 2.24 arrows), compatible with venous drainage of arteriovenous fistula.

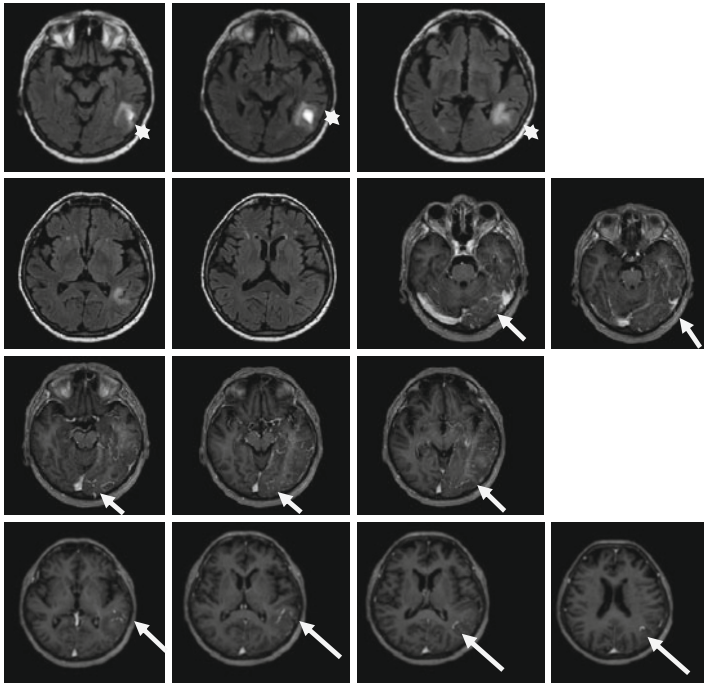


Figure 2.24

The electrocardiogram (ECG) performed in the other hospital showed evidence of an atrial fibrillation which was completely asymptomatic and previously unknown. After medical assessment, anticoagulation therapy was prescribed (full dose of low-molecular weight heparin): on the one hand to treat the atrial fibrillation and on the other hand in view of the possibility that the cerebral hemorrhagic lesion (ICH) might be a hemorrhagic infarct (red infarct) caused by a venous thrombosis of the malformation.

On day 7 it was decided that the patient would be transferred to our stroke unit for endovascular treatment.

A cerebral angiography was performed.

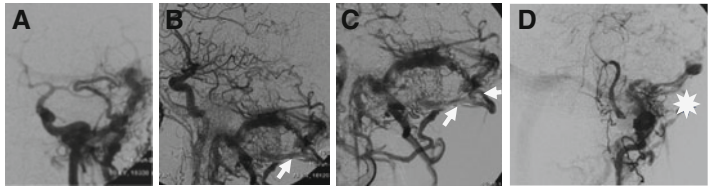


Figure 2.25

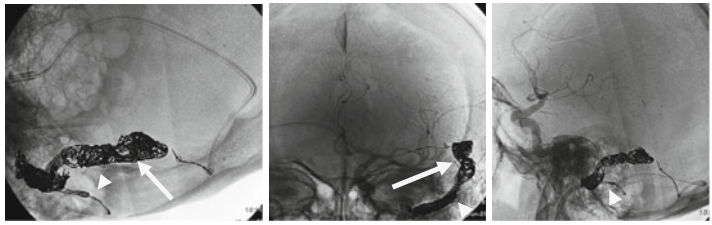


Figure 2.26

The patient underwent a preliminary angiographic scan under general anesthesia (Fig. 2.25), which confirmed the presence of a dural arteriovenous fistula (DAVF) in the left transversus sinus, receiving arterial blood through branches of the left occipital artery (arrow) and of the left vertebral artery (Fig. 2.25D asterisk).

Endovascular treatment was performed (Fig. 2.26).

Coils were inserted (arrow) into the left transversus sinus, followed by perfusion of embolic material (arrow head) to obtain complete occlusion of the origin of the vein and of some arterial feeders.

At the final angiographic scan (Fig. 2.27) a complete exclusion of the fistula was shown. Prior to discharge on day 5 after surgery, the patient was given a neurological examination which revealed no significant deficit and a brain CT scan which showed an initial regression of the edema and of the hematic presence.

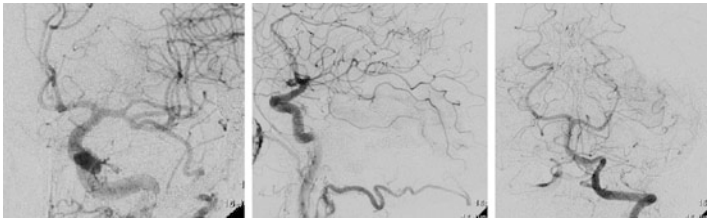


Figure 2.27

2.9 Case Study No. 9

We present the case of a Caucasian female whose medical history revealed birth at 36 weeks due to her mother's malabsorption syndrome which resulted in induced labor, normal mental and physical development, previous surgery to remove a chalazion from the left eye, tonsillectomy, and adenoidectomy. The patient was allergic to dust and cat hair and was being treated with penicillin on a monthly basis due to a previous beta-hemolytic *Streptococcus*-related endocarditic problem (because of this reason, the patient was having regular follow-ups with a cardiologist). The patient was on oral estrogen-progestin therapy for metrorrhagia with regular menstrual cycle. In a state of complete well-being, the patient was struck by an ictal headache in the nuchal area with loss of strength in the right side of the body lasting about 45 min and speech disturbances. The patient was taken to the ED of another hospital where a brain CT scan was performed with contrast. The CT scan showed bleeding in the left basal ganglia associated with SAH due to rupture of an AVM in the front left side, with suspected aneurysm. The patient was transferred to the neurosurgery department of a HUB Hospital and was given an angiography (under general anesthesia in view of prospective endovascular therapy, which was never performed). This confirmed the suspicion of left hemispheric AVM adjacent to the left lateral ventricle with nidus at the caudate, in the area of which a pseudoaneurysmal dilation was detected – the probable cause of the bleed – in addition to a deep venous drainage in the internal cerebral vein.

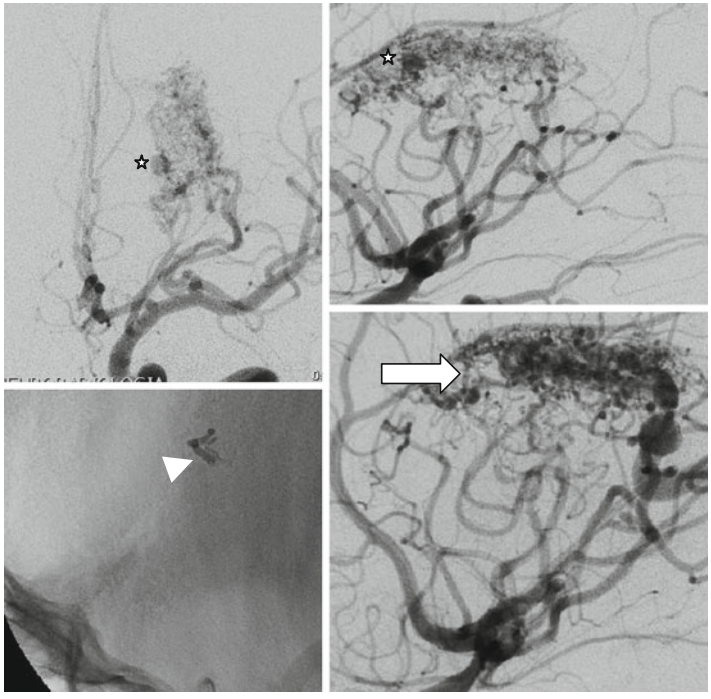


Figure 2.28

The patient was later sent to outpatient rehabilitation. Given the location of the lesion, surgery was not indicated. Three months after the event, the patient was again hospitalized to undergo a combined treatment of endovascular therapy and subsequent radiosurgery with Gamma Knife.

An angiographic study was carried out (Fig. 2.28).

The angiography confirmed the known arteriovenous malformation in the left basal ganglia. The study also showed an intra-nidus angiographic aneurysm, the probable cause of the bleed (star). After inserting a microcatheter into the tributary arterial branch of the aneurysmal dilation, occlusion of the pseudoaneurysm and its tributary branch was carried out through a superselective injection of cyanoacrylate (arrowhead). Follow-up images showed evidence of complete

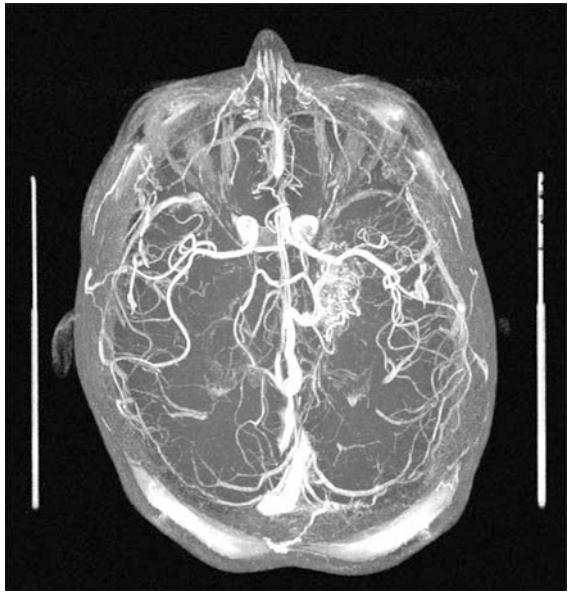


FIGURE 2.29

occlusion of the dilation (arrow). Postoperative progress was regular. The patient then underwent a session of radiosurgery with Gamma Knife, after performing a brain MRI (Fig. 2.29) and angiography with stereotactic helmet for accurate localization of the target (Fig. 2.30).

2.10 Case Study No. 10

We present the case of a 7-year-old Caucasian child who was first observed in the emergency department of another hospital because of the sudden onset of headache; he had also vomited and collapsed to the ground. Instrumental examinations showed

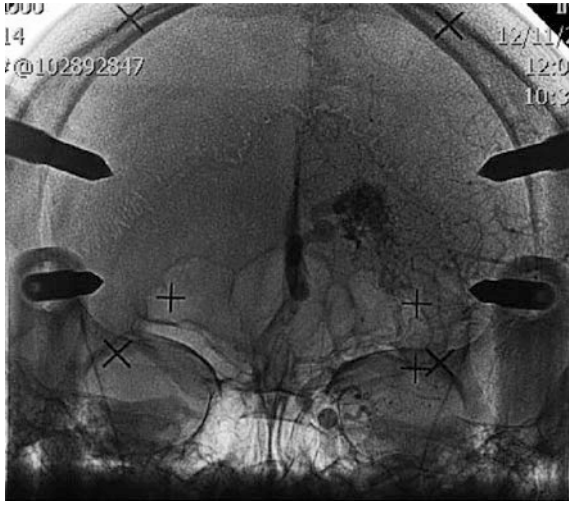


FIGURE 2.30

a right parietal hemorrhage caused by a cerebral arteriovenous malformation. The patient was transferred to our hospital for more detailed examinations and surgery. On arrival in the neurosurgery department, the objective neurological examination showed only an ideomotor slowdown with a tendency to fall asleep unintentionally in the absence of focal deficits. The brain CT scan confirmed the known right parietal cerebral hemorrhage (data not shown).

The day after admission, angiography was performed under sedation (Fig. 2.31).

The angiographic study confirmed the presence of an arteriovenous malformation in the right parietal area (Fig. 2.31A–D see arrows) with both superficial and deep venous drainage and evidence of dislocation of the middle artery branches in the parietal area (Fig. 2.31C asterisk). During hospitalization the patient was stable from a neurological point of view. With a

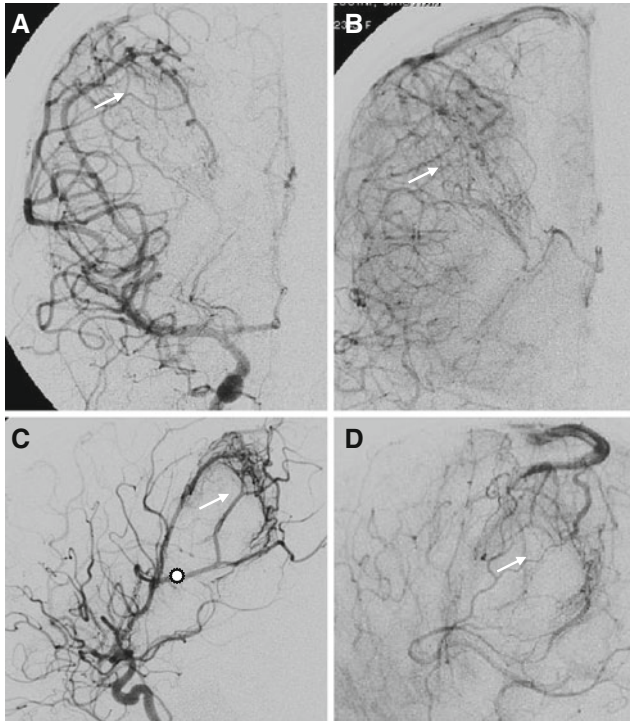


Figure 2.31

view to surgery, an MRI tractography study was carried out to accurately localize the motor pathways (data not shown). The exam confirmed that the known hematoma in the parietal area had not involved the pyramidal tract. After 8 days from haemorrhage, the patient underwent surgery to evacuate the hematoma, exclude the afferent vessels from the nidus of the AVM (branches of the middle cerebral artery) and dissect the lesion. Venous cortical drainage was maintained, which also substituted the normal venous drainage of the surrounding parenchyma. Postoperative progress was regular, with no deficit. The angiography (see picture below) showed complete exclusion of the AVM (Fig. 2.32).

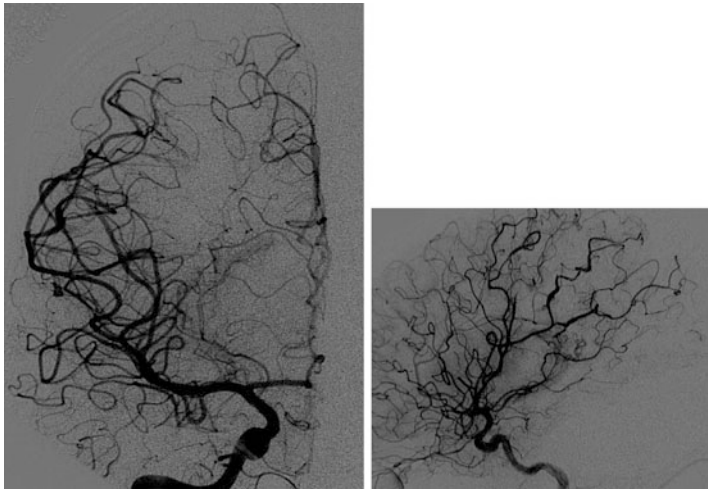


Figure 2.32

Finally, a brain CT study (see picture below) was performed before discharging the patient. It showed no postoperative complications (Fig. 2.33).

The patient was discharged 3 days after surgery; his objective neurological examination was normal.

2.11 Case Study No. 11

We present the case of a 56-year-old South American female with a substantially clear medical history, who was brought to our attention due to the sudden onset of a thunderclap headache.

The neurological clinical examination carried out in the ER was normal except for a stiff neck and testing positive for Kernig's and Brudzinski's signs.

An urgent brain CT scan was carried out (Fig. 2.34).

The CT scan revealed a subarachnoid bleed in the basal cisterns and mainly affecting the left sylvian fissures (asterisk).

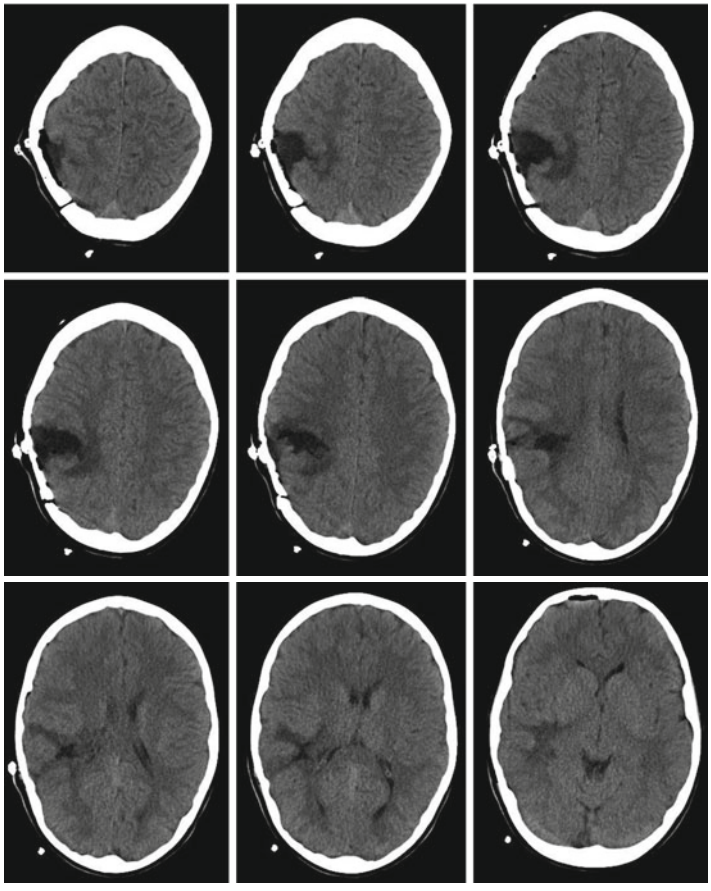


Figure 2.33

An intracranial CT angiogram was performed as a ruptured aneurysm was suspected in the left carotid circulation (Fig. 2.35).

The study of the CT angiogram confirmed the presence of an aneurysmal dilation of the left middle cerebral artery bifurcation with a maximum diameter of 11 mm (Fig. 2.35A *). The patient was admitted to the neurosurgery ward at 02.00 a.m.

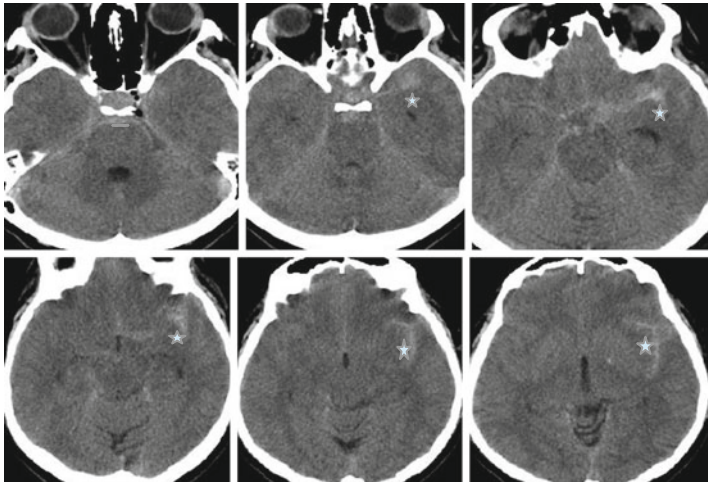


Figure 2.34

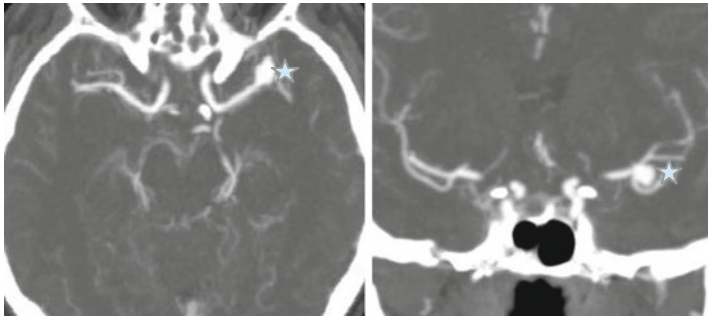


Figure 2.35

(arrival in the ER at 24.00). She was kept under observation and nil by mouth as a brain angiogram was to be performed the following morning (Fig. 2.36).

The angiogram confirmed an aneurysm in the left middle artery (Fig. 2.36, red arrows) with no further dilations of the main branches of the circle of Willis or of the vertebrobasilar

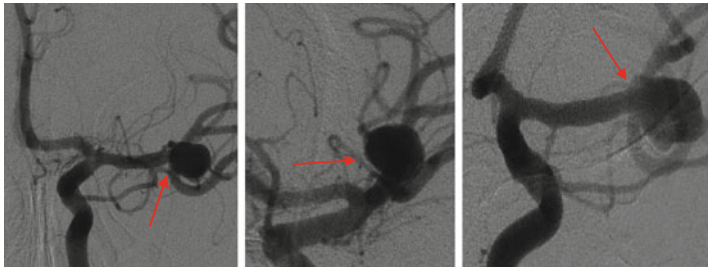


Figure 2.36

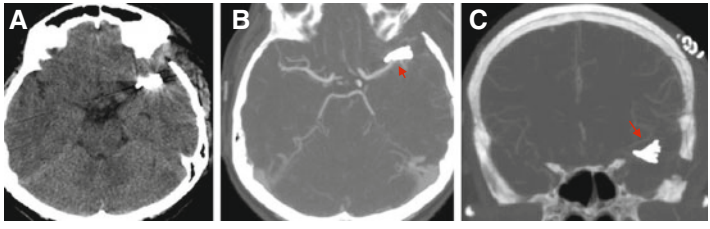


Figure 2.37

circle. After a group discussion, considering the location and the anatomical characteristics of the aneurysm, indication was found for surgical clipping. The patient was prepared for the operation, which took place on the same day without shaving the head (disinfectant shampoo was used). After the operation, the patient was first admitted to the neurointensive care unit for 48 h and then transferred to the neurosurgery ward. She was given oral calcium antagonists as prevention against vasospasms and underwent a series of control Doppler CTs which found no signs of vasospasm. The patient was discharged on day 14 without symptoms. On discharge, the CT angiogram (Fig. 2.37) revealed patency of the branches of the middle cerebral artery near the surgical clips (Fig. 2.37B arrow) and no signs of vasospasm. There were no complications where the craniotomy was performed.

Discussion

Aneurysms located at the middle cerebral artery, ruptured or not, represent the optimum target for surgical approach. Indeed, despite the ISAT trial has shown the superiority of the endovascular approach for ruptured aneurysms, the subgroup of patients with aneurysm at the ACM bifurcation has a better outcome in the surgical group [3].

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Chapter 3
Clinical Organizational Pathways for Hemorrhagic Stroke

Valentina Oppo and Valentina Perini

Hemorrhagic stroke is a medical emergency and requires prompt management because of the high risk of rapid deterioration in the patient's general condition. In fact, more than 20 % of patients show a rapid decrease in the Glasgow Coma Scale (GCS) score, which can be reduced by two points or more in the first hours after onset of symptoms [1].

3.1 Management

3.1.1 Prehospital Management

It is recommended that rescue personnel are adequately trained to recognize stroke signs early on and to manage the patient at this stage, during which the following are necessary:

- Airway, breathing, circulation assessment
- Vital signs detection (breathing, pulse, blood pressure, O_2 saturation)
- GCS score
- Cincinnati Prehospital Stroke Scale (CPSS)
- Transportation of the patient to the nearest and most suitable hospital for stroke management [2]

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Furthermore, it is important to collect essential informations such as the time of onset of symptoms and medical and pharmacological history.

3.1.2 In-Hospital Management

American Heart Association / American Stroke Association (AHA/ASA) (class I, level B) recommends using assessment tools in order to quantify objectively the severity of each individual case [3]. The National Institutes of Health Stroke Scale (NIHSS) could be a valuable tool [4, 5]. However, patients with cerebral hemorrhage suffer from an altered state of consciousness, and this aspect limits the usefulness of the NIHSS. For this reason it seems more appropriate to use the ICH score [6, 7].

Clinical presentation alone is not sufficient to differentiate hemorrhagic stroke from ischemic stroke, as both are characterized by acute onset of neurological symptoms. However, there are some elements that can point to hemorrhagic stroke: severe headache, vomiting, Blod Pressure (BP) systolic values > 220 mmHg, level of vigilance reduced even to coma level, and progression of symptoms within hours or minutes [8].

For the differential diagnosis of acute ischemia and cerebral hemorrhage, the brain CT scan is still considered the gold standard according to the guidelines of the leading national and international scientific societies (AHA/ASA, European Stroke Organization (ESO); Stroke Prevention an Educational Awareness Diffusion (SPREAD)) [3, 9, 10]. In fact, although gradient echo and T2 susceptibility-weighted MRI is more sensitive than CT scan in identifying hyperacute cerebral hemorrhage [11, 12], its use is limited by several factors including execution time, cost, distance from the emergency area, and patient intolerance [13].

Intraparenchymal brain hemorrhage may be primary (80 % of cases, associated with hypertension or amyloid angiopathy) or secondary (associated with arteriovenous malformations (AVMs), aneurysms, tumors, cerebral venous thrombosis). Since this difference involves some prognostic

and therapeutic implications, a more detailed diagnosis is needed if a secondary form is suspected.

The AHA/ASA guidelines suggest which factors should raise suspicion for a secondary hemorrhage and which are the most appropriate investigations: [3] young age (<65 years); female gender; absence of risk factors such as cigarette smoking, hypertension, or coagulopathy; atypical location of the lesion (lobar); or intraventricular hemorrhage extension [14, 15].

The following medical examinations must be carried out if a more detailed diagnosis is needed: brain MRI, Magnetic Resonance Angiography (MRA), and CT angiography with venous sequences. If there is a high clinical or radiological suspicion, DSA is recommended (class IIa, level of evidence B-AHA/ASA) [3].

The high percentage of patients who suffer early clinical deterioration after the onset of cerebral hemorrhage is partly due to the increase in hematoma volume during the first hours. Such an event negatively influences the prognosis and is associated with an increased risk of mortality. It is therefore important to identify patients at high risk of hematoma expansion.

For this purpose, the AHA/ASA guidelines (class IIB, level of evidence B) recommend that CT angiography and brain CT scan are performed with contrast medium [3], which allows detection of the so-called spot sign, i.e., contrast medium uptake in the area of the hematoma, whose presence correlates with the risk of the hemorrhagic lesion expanding [16, 17].

The AHA/ASA guidelines suggest that a panel of standard blood tests are performed in emergency in the case of cerebral hemorrhage [3]: blood count, serum electrolytes, urea, creatinine, blood glucose (hyperglycemia is associated with a worse outcome), liver function, International Normalized Ratio (INR), activated partial thromboplastin time (aPTT) (useful for determining the level of coagulation, especially in patients on anticoagulant therapy), and troponin (an increase in troponin has proven to be associated with a worse outcome) [18, 19].

Once the patient has been diagnosed, the ESO guidelines recommend prompt admission to a stroke or intensive care unit with dedicated medical and nursing staff [9]. Patients treated in

these specific *settings* show lower mortality and disability rates compared to patients admitted to general wards [20].

However, few centers have developed specific management protocols for ensuring that treatment of hemorrhagic stroke is initiated rapidly, in comparison to treatment of ischemic stroke. The Neurocritical Care Society emphasizes the usefulness of prompt treatment of hypertension and coagulopathy, which must already be started in the emergency department [21].

3.2 Medical Treatment

3.2.1 Hemostasis and Coagulation

Cerebral hemorrhage frequently occurs in patients receiving anticoagulant or antiplatelet therapy and in patients suffering from congenital or acquired deficiency of clotting factors or congenital or acquired quantitative or qualitative platelet abnormalities.

For patients with deficiency of coagulation factors or platelet disorders, AHA/ASA guidelines recommend the infusion of involved factors in the first case and of platelets in the second (class I, level of evidence C) [3].

It is not yet clear which is the cutoff value of platelets, below which the transfusion of platelet concentrates is recommended. According to the SPREAD guidelines, 50,000/mm^3 should be considered the cutoff [10], although cases must be evaluated individually since there may be conditions which require transfusion for higher values (patients requiring neurosurgery, particularly extensive hemorrhage).

For patients on intra venous (IV) heparin therapy, IV administration of protamine sulfate is recommended at a dosage of 1 mg/100 U of heparin (maximum dose 50 mg). The dose must be corrected according to the time elapsed since administration of the heparin (class IIb, level of evidence C – AHA/ASA) [3, 22]. Similar doses may be administered to patients on low molecular weight heparin therapy (LMWH), but their effectiveness in reversing the effect of the drug may be incomplete [21].

If the brain hemorrhage occurs in a patient on anticoagulant therapy with vitamin K antagonists, the administration of vitamin K is definitely indicated (class I, level of evidence C – AHA/ASA) [3], but its effect on the correction of INR is not evident in the early hours after administration. The vitamin starts to work 2 h after administration and reaches maximum effect 24 h afterward [23].

For immediate correction of INR, fresh frozen plasma can be used. Fresh plasma needs *cross matching* and is associated with the risk of allergic reaction or transmission of viral infections. Furthermore, very high volumes of plasma are often needed [24].

Prothrombin complex concentrate (PCC) is available both in a 3-factor formulation (II, IX, X) and in a 4-factor formulation (which also contains the VII). It requires no *cross matching*, can be administered quickly and in small volumes (20–40 ml), and is very fast in normalizing INR (within minutes) [25].

This profile of safety and efficacy according to the AHA/ASA is preferable to fresh frozen plasma (class IIb, level of evidence B) [3]. There is an associated risk of thrombotic events, but it is not particularly high [25].

The recombinant activated factor VII (rFVIIa) quickly normalizes INR, but it does not replace all the vitamin K-dependent factors, nor does it restore adequate thrombin generation [26]. For this reason it is not recommended by the AHA/ASA guidelines (class III, level of evidence C) [3].

Instead, ESO 2014 guidelines emphasize the absence of trials that directly compare the effectiveness of fresh frozen plasma, prothrombin complex, and rFVIIa, and therefore they do not give any recommendation on the type of hemostatic agent to be used [9].

There is no unanimous opinion about the target INR value to be reached: it ranges from <1.3 to <1.5 [27].

For patients treated with the new oral anticoagulants, there are currently no pharmacological agents that have been proven effective in reversing these molecules. Activated carbon is effective in reducing absorption of the drug, if the last dose was taken within two hours. PCC and rFVIIa seem to be

useful in reversing the activity of direct thrombin inhibitors (dabigatran) [28].

Hemodialysis has been suggested as an effective option for removing dabigatran, but is less effective on rivaroxaban and apixaban because of their high protein binding (class IIb, level of evidence C – AHA/ASA) [3]. The ESO guidelines do not express any recommendation because of the scarcity of studies on the subject [9].

Some studies have investigated the efficacy of rFVIIa on intracranial hemorrhages in patients who were not taking anticoagulant or antiplatelet therapy. Although a limitation in the extension of hematoma volume was observed, which was associated with a better clinical outcome, this method is not recommended in AHA/ASA, ESO, and SPREAD guidelines (class III, level of evidence A – AHA/ASA) [3, 9, 10] as it involves an excessive risk of thromboembolism [29].

As for the prophylaxis of deep vein thrombosis (DVT), there is no indication for the use of elastic graduated compression stockings. The recent CLOTS3 study has demonstrated the effectiveness of the use of intermittent pneumatic compression [30] which in fact is included in the recommendations of ESO and AHA/ASA guidelines (class I, level of evidence A) [3, 9].

According to AHA/ASA guidelines, the administration of LMWH can be taken into consideration once it has been documented that the bleeding has stopped, 4–5 days after onset of the hemorrhage [3], while ESO 2014 guidelines emphasize the fact that there is no evidence of the benefits of prophylaxis with LMWH and that no conclusive indication can be derived from available studies regarding the timing of its introduction [9]. It seems that such therapy is not associated with an increased risk of hemorrhage [31].

AHA/ASA (class IIa, level of evidence C) guidelines recommend the administration of systemic anticoagulants or the use of indwelling or temporary vena cava filter if

there is symptomatic DVT or pulmonary embolism during brain hemorrhage [3]. The choice between these two options depends on several factors: the time elapsed from onset of hemorrhage, the stability of the hematoma, the cause of the hemorrhage, and the overall clinical condition of the patient [32].

3.2.2 Controlling Hypertension

High blood pressure is common in patients with cerebral hemorrhage and it is due to various factors: preexisting hypertension, neuroendocrine response to stress, and response to increased intracranial pressure. This condition can cause an increase in hematoma volume, deterioration of neurological conditions, increased mortality rate, and risk of disability [33].

It has been documented that performing perfusion CT on patients who are undergoing intensive treatment for hypertension (systolic BP target <140 mmHg) does not show any reduction of blood flow in the area around the hematoma [34]. In the INTERACT studies 1 and 2, the safety and efficacy of aggressive blood pressure treatments (with Systolic Blood Pressure (SBP) target <140 mmHg), during the early stages of cerebral hemorrhage, was compared with the standard treatment (with target SBP <180 mmHg). The studies demonstrated that this approach is safe, and furthermore the patients who received the more aggressive treatment achieved better functional recovery and a better quality of life. There is no evidence however of a positive impact on the increase in hematoma volume [35, 36].

Based on the results obtained, the AHA/ASA 2015 and ESO 2014 guidelines consider the intensive treatment of hypertension to be safe and potentially effective (class I, level of evidence A) [3, 9].

According to AHA/ASA guidelines, reaching the target 140 mmHg is probably not very feasible for patients with initial

SBP > 220 mmH [3]. In this case they recommend an aggressive treatment to reduce blood pressure by continuous intravenous infusion of drugs, with continuous monitoring of BP.

SPREAD 2012 guidelines contain the following recommendations: [10]

- SBP > 200 mmHg or mean BP > 150 mmHg: aggressive treatment with intravenous medications in continuous infusion, BP monitoring every 5 min
- SBP > 180 mmHg or mean BP > 130 mmHg with evidence or suspicion of intracranial hypertension: intravenous continuous infusion or bolus
- SBP > 180 mmHg or mean BP > 130 mmHg with no clinical suspicion of intracranial hypertension: continuous intravenous infusion or bolus aimed at slightly reducing blood pressure (SBP 160 mmHg, 110 mmHg WFP); the clinical status of the patient must be reassessed every 15 min

The AHA/ASA guidelines make no specific recommendations regarding the pharmacological agent to be used [3], while SPREAD guidelines mention labetalol, urapidil, furosemide, and nitroprussiate, all medications administered intravenously in divisible doses [10].

3.2.3 Managing Glycemia

High blood glucose levels at onset of cerebral hemorrhage are correlated with an increased risk of death and disability; correction is therefore recommended in patients without diabetes [37]. However, treatment with continuous infusion of insulin is not indicated since it involves an excessive risk of hypoglycemia.

It is still unclear which blood glucose target to maintain in the acute phase, but it is advisable to monitor patients closely (three times a day), even those without diabetes, in order to avoid both hyper- and hypoglycemia (class I, level of evidence C – AHA/ASA) [3]. Correction with insulin is always indicated for blood glucose values > 200 mg/dl.

3.2.4 Managing Body Temperature

Hyperpyrexia has proven to be an independent negative prognostic factor [38]. Despite this premise, it has not been demonstrated that drug treatment benefits outcome in real terms [39].

The AHA/ASA guidelines recognize a level of evidence C for the treatment of hyperpyrexia [3]. ESO guidelines are aligned with respect to early treatment while explicitly advising against the preventive treatment of hyperpyrexia outside clinical trials [9].

3.2.5 Treating Epileptic Seizures

The frequency of epileptic seizures during cerebral hemorrhage is approximately 16 %. They mainly occur during the first week after onset and when there is lobar hemorrhage [40, 41].

Prophylactic treatment with antiepileptic drugs is not recommended as it may result in a worsening of outcome (class II, level of evidence B – AHA/ASA) [3]. SPREAD and AHA/ASA guidelines recommend drug treatment for seizures (class I, level of evidence A – AHA/ASA) [3, 9] which are detected by an EEG recording in patients with impaired consciousness (class I, level of evidence C – AHA/ASA) [3], even when the seizures are subclinical. Continuous Electro Encephalo Gram (EEG) monitoring is therefore recommended in patients who have a reduced state of consciousness that cannot be justified on the basis of the hematoma's characteristics (class IIa, level of evidence C – AHA/ASA) [3].

3.2.6 Managing Medical Complications

The most common complications are pneumonia (5.6 %), aspiration (2.6 %), respiratory failure (2 %), pulmonary embolism (1.3 %), and sepsis (1.7 %). Approximately 50 % of deaths after

stroke are due to medical complications. Dysphagia is the main risk factor for pneumonia, so AHA/ASA guidelines recommend assessment of swallowing disorders using a standardized test such as the water swallowing test (class I, level of evidence B) [3, 42].

The detection of high levels of troponin during the first 24 h after admission (about 15 % of patients) is associated with increased mortality; AHA/ASA guidelines therefore recommend screening for myocardial ischemic events by performing ECG and dosing troponin (class IIa, level of evidence C) [3].

3.2.7 Monitoring and Managing Intracranial Hypertension

Intracranial hypertension is due to hydrocephalus from ventricular flood or mass effect of the hematoma. For this reason, if the hematomas are small and there is minimum ventricular flooding, no treatment is needed.

Intracranial pressure (ICP) can be measured by means of either parenchymal or ventricular catheters; if necessary, the latter can also be used to drain fluid. These devices, particularly ventricular catheters, carry the risk of rebleeding or infectious complications.

Increase in intracranial pressure and decrease in cerebral perfusion pressure are related to a higher mortality rate and worse functional outcome [43]. In the absence of studies that clearly define the indication for ICP monitoring, AHA/ASA and SPREAD guidelines recommend monitoring and possibly treating intracranial pressure in patients with GCS score <8 related to the mass effect of the hematoma and if there is high-severity ventricular flooding, hydrocephalus, or clinical manifestations of transtentorial herniation (class IIb, level of evidence C – AHA/ASA) [3, 10].

The ESO 2014 guidelines point out that in the absence of randomized controlled trials, it is impossible to formulate an indication for ICP monitoring [9]. They also highlight that a low rate of complications has been reported [44].

If there is intracranial hypertension, the AHA/ASA guidelines strongly recommend the following therapy: [3] elevate the patient's head 30° above the bed and administer a mild sedation; avoid the use of collars or devices that compress the neck veins; and use osmotic agents such as mannitol or hypertonic solutions, which are considered more effective [45]. Corticosteroids, on the other hand, are considered to be contraindicated (class III, level of evidence B) [3].

In the case of hydrocephalus secondary to obstruction of the flow of cerebrospinal fluid, CSF drainage may be considered, especially in patients with a reduced level of consciousness (class IIa, level of evidence B – AHA/ASA) [3].

3.3 Surgical Treatment

3.3.1 Intraventricular Hemorrhage

Intraventricular hemorrhage occurs in about 45 % of cases of intracerebral hemorrhage. Drainage via a ventricular derivation catheter may be useful; it is however often ineffective due to the difficulty in maintaining patency. To overcome this obstacle, fibrinolytic drugs can be administered intraventricularly recombinant tissue Plasminogen Activator (rtPA), but they may increase the risk of rebleeding.

Endoscopic evacuation has been used as an alternative. However, the safety and effectiveness of this procedure have not yet been proven [46, 47].

Because of the absence of firm evidence of their effectiveness, the AHA/ASA guidelines assign a level B evidence [3] both to endoscopic treatment and to intraventricular administration of fibrinolytics [46, 47].

3.3.2 Surgical Treatment of Cerebral Hemorrhage

There is no clear evidence that surgery offers better results compared to the medical treatment of supratentorial

parenchymal hemorrhages [48]. In fact, according to SPREAD and AHA/ASA guidelines, surgical treatment of supratentorial hemorrhage should be limited to cases where the patient's neurological status deteriorates (class IIb, level of evidence A – AHA/ASA) [3, 10].

Furthermore, according to AHA/ASA guidelines, the evacuation of supratentorial hematoma in patients who suffer rapid neurological deterioration should be considered a lifesaving measure (class IIb, level of evidence C) [3].

On the other hand, based on the results of one meta-analysis [49], ESO guidelines suggest that, if performed early, surgery might offer greater benefits for patients with a better state of vigilance (GCS 9–12) [9].

As for cerebellar hemorrhages, surgical evacuation of hematoma is unanimously recommended for patients who are likely to suffer from neurological deterioration or brain stem compression [50] (class I, level of evidence B – AHA/ASA) [3].

It is also highlighted that applying Cerebrospinal Fluid (CSF) drainage as the first phase of treatment is contraindicated (class III, level of evidence C – AHA/ASA) [3]. Unlike cerebellar hemorrhage, evacuation of brain stem hemorrhage can be a harmful procedure.

Decompressive craniectomy, with or without evacuation, could reduce mortality in patients suffering from supratentorial bleeding with one or more of the following characteristics: coma, large hematoma with midline shift, and high intracranial pressure refractory to other medical therapies.

However, there are not sufficient data available in literature to determine its effectiveness [51] (class IIb, level of evidence C – AHA/ASA) [3].

3.4 Secondary Prevention

The annual risk of recurrent cerebral hemorrhage goes from 1 to 5 % [52, 53]. The main risk factors are high blood pressure, older age, and lobar hemorrhage. The fact that the risk increases with age appears to be attributable to the higher

prevalence of amyloid angiopathy (responsible for recurrent bleeding in the lobar locations) and increased use of antithrombotic drugs. Other risk factors are ε2 and ε4 allele of apolipoprotein E and the presence of multiple microbleeds, especially in the lobar locations, on *gradient echo* MRI.

3.4.1 Control of Hypertension

The PROGRESS study shows that reducing blood pressure (with perindopril and indapamide) decreases the risk of recurrence of cerebral hemorrhage, as well as other vascular events [54].

The Secondary Prevention of Small Subcortical Strokes (SPS3) study shows that maintaining systolic blood pressure <130 mmHg reduces the risk of recurrence, especially in patients suffering from known small vessel disease [55]. AHA/ASA and ESO guidelines therefore recommend controlling blood pressure as secondary prevention (class I, level of evidence A – AHA/ASA) [3, 9].

The best time to start treatment remains unclear, although the INTERACT2 study has demonstrated that it is safe to start treatment early [36].

3.4.2 Management of Anticoagulation and Antiplatelet Treatments

There are no randomized trials that give indications about when to reintroduce anticoagulant therapy after a hemorrhagic cerebral event. The decision must be made by assessing the relationship between hemorrhagic risk and thromboembolic risk in each individual patient.

The indications of the SPREAD 2012 guidelines are as follows [10]:

- Absolute contraindications to resuming oral anticoagulation therapy (OAT): lobar hemorrhage correlated to amyloid angiopathy.

- Resume OAT 3 weeks after the event for patients at high thromboembolic risk: mitral mechanical valve prosthesis, thrombosis of the heart chambers, and arterial and venous thromboembolism in the previous 30 days.
- Restart OAT after the 30th week for patients at high risk of bleeding because of the presence of microbleeds on *gradient echo* MRI, presence of leukoaraiosis, and lobar hemorrhages not correlated with amyloid angiopathy.

  Restart OAT between the 10th and the 30th week: in all other cases, such as deep brain hemorrhage.
  Only for patients with atrial fibrillation at high thromboembolic risk and absolute contraindication to resuming OAT can be considered percutaneous closure of the left atrium.

AHA/ASA guidelines suggest avoiding administration of warfarin for patients suffering from non-valvular atrial fibrillation and previous warfarin-related lobar hemorrhage (class IIa, level of evidence B) [3]. As regards when to resume therapy, the guidelines suggest 4 weeks unless the patient has a mechanical heart valve (class IIb, level of evidence B) [3].

ESO guidelines do not give any suggestions regarding indications and appropriate timing for resuming anticoagulation therapy after cerebral hemorrhage and highlight the need for randomized trials on the topic [9].

There are no accurate data regarding resumption of antiplatelet therapy. However, the risk of myocardial infarction and ischemic stroke is higher than the risk of rebleeding in both deep and lobar locations [56]. According to AHA/ASA guidelines, therefore, therapy may if necessary be reintroduced the day after the cerebral hemorrhage (class IIa, level of evidence B) [3].

No advantage has been demonstrated in using the new oral anticoagulants (dabigatran, rivaroxaban, apixaban) as opposed to administering warfarin to patients with previous brain

hemorrhage, who are suffering from non-valvular atrial fibrillation [57] (class IIb, level of evidence C – AHA/ASA) [3].

Lifestyle changes must also be made by avoiding alcohol, giving up smoking, and correcting the syndrome of obstructive sleep apnea (class IIa, level of evidence B – AHA/ASA) [3].

The SPARCL study has shown that administering high-dose atorvastatin reduces the risk of ischemic stroke but increases the risk of hemorrhagic stroke. However there is no reliable data regarding the need to reduce the use of statins in patients with cerebral hemorrhage [58] (class IIb, level of evidence C – AHA/ASA) [3].

3.5 Subarachnoid Hemorrhage

3.5.1 Initial Evaluation

Three variables are closely related to the prognosis of patients with subarachnoid hemorrhage (SAH): neurological condition on admission, age, and the amount of blood visible on the CT.

The Hunt and Hess scale is currently widely used for initial evaluation. However, it is considered to have a low level of inter- and intra-observer agreement and an unsatisfactory correlation with outcome [59]. As the scales based on the GCS are more reliable, a committee of the World Federation of Neurological Surgeons (WFNS) proposed a scale essentially consisting of the GCS, with additional points relating to focal deficits to be assigned to patients with GCS 14 or 13.

Another scale is "Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage" (PAASH), also based on the GCS [60]. ESO guidelines dated 2013 recommend the use of scales based on the GCS in the initial assessment of SAH patients, especially recommending the PAASH scales (class III, level of evidence C) [61].

3.5.2 Diagnosis

Brain CT scan is the imaging method recommended by guidelines (AHA/ASA, ESO, and SPREAD) [10, 61, 62]; it is particularly sensitive within the first few hours after onset of symptoms. In fact, if the sensitivity within the first three days is almost 100 %, it is significantly reduced after 5–7 days, due to reabsorption and redistribution of volume of blood [63].

In such cases a brain MRI may be performed (in particular FLAIR, proton density, Diffusione Weighted Imaging (DWI) and gradient echo sequences); however, this method is not very suitable in emergency (length of the examination, high sensitivity to artifacts caused by movement, lack of tolerance by patients, contraindication in pacemaker carriers) [64].

If the brain CT scan (and if necessary the MRI) does not supply critical diagnostic information, but an SAH is strongly suspected, a lumbar puncture must be performed (class I, level of evidence B – AHA/ASA; class II, level of evidence B – ESO) [61, 62], preferably between 6 and 12 h after the event. In this phase, due to the processes of hemoglobin degradation, it is easier to encounter xanthochromic rather than frankly hematic liquor.

The search for the aneurysm at the source of the hemorrhage can rely on CT angiography, MRA, and DSA. However, CT angiography is not able to detect small aneurysms (diameter <3 mm). If the CT angiography for detecting aneurysms is negative, and there persists a strong suspicion of aneurysmal SAH, the AHA/ASA and ESO guidelines recommend performing angiography (class IIb, level of evidence C – (AHA/ASA); class II, level of evidence B(ESO)) [61, 62, 65].

According to European guidelines (ESO) it would also be appropriate to repeat CT angiography or DSA after at least 3 weeks, if the previous tests were negative (class III, level of evidence B) [61].

If there is a perimesencephalic SAH pattern, CT angiography and MRI angiography have demonstrated high sensitivity in excluding the presence of an aneurysm. According to

the AHA/ASA guidelines, if these tests do not detect an aneurysm, cerebral DSA may not be necessary [62].

According to ESO guidelines, however, no reliable data is available to justify the decision not to perform DSA [61]. If the DSA is negative, it is inappropriate to repeat it after a short time, as the risks connected to the procedure outweigh the possibility of actually finding an aneurysm [66].

The type of treatment of an aneurysm may be based on the data obtained by noninvasive methods such as CT angiography, but this can lead to erroneous conclusions, often overestimating the size of the neck of the aneurysm itself and therefore concluding that it is unsuitable for endovascular treatment.

According to the AHA/ASA and SPREAD guidelines [10, 62], cerebral DSA provides the best anatomical description of the aneurysm with high spatial resolution, useful for planning an intervention and choosing the most appropriate treatment for each individual case (class I, level of evidence B) [67].

3.5.3 Medical Management

According to ESO guidelines, the patient must be observed for the first 7 days in an intensive care unit, where continuous observation can be carried out with frequent monitoring of ECG, state of consciousness, pupil size and onset of focal deficits, body temperature, and water balance [61].

Headache can be controlled by administering paracetamol. Salicylates must be avoided because of their anti-hemostatic effect. If pain is particularly intense, the use of opiate drugs must be taken into consideration.

Before closing the aneurysm, situations that lead to increased intracranial pressure must be avoided. The patient must be kept in bed, using antiemetic drugs and laxatives (measure of *good clinical practice* (GCP) according to ESO guidelines) [61].

AHA/ASA and ESO guidelines agree on establishing an indication for the control of hyperglycemia and hyperthermia [61, 62].

Adequate blood pressure control should guarantee a low risk of rebleeding and secondary ischemic events by maintaining appropriate values of cerebral perfusion pressure. There are no certain data regarding the optimal blood pressure target to be achieved.

According to ESO guidelines, it would be appropriate to maintain systolic blood pressure at <180 mmHg (GCP) before obliterating the aneurysm [61]. The AHA/ASA guidelines consider as appropriate all values that remain below 160 mmHg (class IIa, level of evidence C) [62].

Intermittent pneumatic compression devices are indicated for the prevention of thromboembolic events, especially prior to treating the aneurysm (class II, level of evidence B – ESO) [61]. According to ESO guidelines, the use of LMWH in prophylactic doses must not be taken into consideration until 12 h has elapsed from surgery and from endovascular treatment [61, 68].

The incidence of seizures ranges from 6 to 18 %. The risk factors are aneurysm of the middle cerebral artery, large volume of blood in the subarachnoid space, the presence of intracerebral hematoma, rebleeding, ischemic events, severe neurological impairment, and a history of high blood pressure prior to the SAH. The prophylactic use of Anti-Epileptic Drugs (AEDs) is a very common practice, based on the assumption that the occurrence of seizures in the early stages can cause additional neurological damage, although there is no evidence of its effectiveness (class IIb, level of evidence B – (AHA/ASA); class IV, level of evidence C – (ESO)) [61, 62]. In fact, it has been observed that the use of AEDs in prophylaxis is associated with a worse outcome [69].

In case of a clinically manifest seizure, appropriate drug treatment is necessary [70] (GCP according to ESO guidelines) [61].

Both hyper- and hyponatremia are common conditions with SAH. Hyponatremia is often secondary to excessive

secretion of natriuretic peptide. The AHA/ASA guidelines recommend using hypertonic saline and a mineralocorticoid in order to increase blood flow and cerebral oxygenation (class IIa, level of evidence B) [62, 71]. According to the ESO guidelines, however, there is inadequate evidence regarding the efficacy of treatment with mineralocorticoids [61].

Antifibrinolytic therapy with tranexamic acid or aminocaproic acid was used in some randomized trials: the therapy reduced the risk of rebleeding, but had no effect on mortality or prognosis [72].

Although the US Food and Drug Administration has not approved the administration of such drugs to prevent rebleeding, the AHA/ASA and SPREAD guidelines [10, 62], unlike ESO guidelines [61], consider the use of these drugs reasonable in those patients who are eligible for aneurysm treatment but who, in the absence of specific medical contraindications, cannot be treated immediately, at least not until 72 h has elapsed from the event (class IIa, level of evidence B – AHA/ASA).

3.5.4 Treatment of Aneurysms

The treatment options available are as follows: surgical treatment (clipping) or obliteration by endovascular coils (coiling), to be performed as early as possible in order to reduce the risk of rebleeding (class I, level of evidence B – AHA/ASA) [62]. Clipping was the primary mode of treatment until 1991, when Guglielmi first described endovascular treatment by means of spirals.

ISAT is the only multicenter randomized trial which has compared the two techniques in patients who were eligible for both types of treatments. Follow-up in the short term (1 year) shows that in patients undergoing endovascular treatment, the risk of death and disability is lower than in patients undergoing surgical treatment (23.7 % and 30.6 %, respectively) [73].

The medium-term follow-up (9 years) shows that the risk of rebleeding and recurrence of the aneurysm is higher in patients who were treated with coiling, resulting in a greater need to repeat surgery (17.4 % versus 3.8 % of patients treated with clipping), but without this leading to a worse clinical outcome [74].

In 2015, the long-term follow-up data (18 years) concerning the UK cohort study by ISAT were published: coiling is associated with a small increase in the risk of SAH recurrence. However, the chances of maintaining a good level of independence (modified Rankin Scale score: 0–2) are significantly greater for this group of patients [75].

There have been many criticisms of this study as the population is considered overly selective. In fact, the study excludes patients with aneurysms > 1 cm, located in the vertebrobasilar circulation, age > 70 years, and with high WFNS degrees. To address these criticisms, the ISAT II study was developed: a multicenter international trial involving 50 centers which started in 2012 and are currently recruiting patients. This study will be concluded in 2024.

The cerebral aneurysm re-rupture after treatment study shows that the risk of recurrence of aneurysm rupture is greater when the patient is treated with coiling [76].

The AHA/ASA guidelines highlight that the choice of the most suitable treatment for each case should be a multidisciplinary decision (class I, level of evidence C) [62]. All major guidelines agree on the need to act as quickly as possible (SPREAD and ESO recommend treatment within 72 h of onset) [10, 61].

If the aneurysm is eligible for both treatments, coiling is the preferred one (class I, level of evidence A – (ESO); class I, level of evidence B – (AHA/ASA) [61, 62].

The choice depends on certain factors regarding the patient (age, comorbidities, presence of intraparenchymal hematoma, SAH grade, size, location, and shape of the aneurysm) and procedures (technical skills, and availability of the operators).

Factors in favor of surgical treatment are young age, milder clinical severity, presence of intraparenchymal hematoma, localization in the middle cerebral artery, wide aneurysm neck, and presence of arterial branches originating directly from the aneurysm sac.

Factors in favor of endovascular treatment are age > 70 years (the risk of recurrence is less important than in young people), intermediate and high clinical degrees (3–4) on Hunt and Hess scale, aneurysm of the basilar artery or posterior circle, tight aneurysm neck, and single-lobe aneurysm.

In view of the risk of the aneurysm recurring, especially in patients undergoing embolization with coils, an angiographic follow-up must be carried out over time.

According to SPREAD guidelines, closing of the afferent vessel is indicated, after an occlusion test, when elective surgical or endovascular treatments are not possible [10].

3.5.5 Management of Hydrocephalus

Hydrocephalus is a complication caused by an obstruction of the flow of, or reabsorption of, cerebrospinal fluid. In a third of cases, it remains asymptomatic and, in half of the patients who undergo changes in their level of consciousness, improves spontaneously within 24 h. In patients with evidence of symptomatic hydrocephalus, an external ventricular shunt (EVD) or drainage through lumbar puncture must be carried out (class I, level of evidence B – AHA/ASA) [62, 77, 78].

The latter procedure requires special care because of the risk of transtentorial herniation in patients with severe intracranial hypertension (intraparenchymal hematoma) (class IV, level of evidence C – ESO) [61]. EVD increases the risk of infectious complications and rebleeding. In patients with symptomatic chronic hydrocephalus, a permanent ventricular shunt is recommended (class I, level of evidence C – AHA/ASA) [62].

3.5.6 Prevention of Vasospasm

Vasospasm occurs very frequently between 7 and 10 days after onset and resolves spontaneously after 21 days. Ischemic events related to it are the leading cause of death and disability in SAH patients.

All major guidelines (AHA/ASA, ESO, SPREAD) agree on the efficacy of nimodipine (60 mg orally every 4 h for 3 weeks) in the prevention of vasospasm (class I, level of evidence A) [61, 62, 79].

Diagnosis and monitoring can be carried out by means of Transcranial Doppler, CT, or MRI perfusion [80].

Once a diagnosis has been reached, the first intervention consists in hemodynamic support, which is no longer based on the "historical" approach of triple H (hemodilution, hypertension, hypervolemia). Nowadays it is believed that the only truly effective measure of these three is maintenance of a moderate hypertensive state, unless there are contraindications (class I, level of evidence B – AHA/ASA) [62, 81].

According to SPREAD guidelines, magnesium sulfate and statins are recommended for preventing vasospasm, but their effectiveness has not been unequivocally demonstrated [10]. The ESO guidelines do not on the other hand recommend the use of magnesium sulfate (class I, level of evidence A) [61].

For patients who do not respond to noninvasive treatments, cerebral angioplasty or intra-arterial infusion of vasodilatator agents (calcium channel blockers) can be performed by angiography (class IIa, level of evidence B – AHA/ASA) [62, 82].

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Chapter 4
Differentiated Decisional Algorithms

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This chapter presents some algorithms for decision-making, inspired not only by the clinical aspects but also by the organizational, technological, and professional characteristics of the hospital receiving and caring for the acute stroke patients. A summarizing table (*decisional algorithm*, Table 4.1) classifies the various settings (A, B, C, D) in which clinicians manage patients. These algorithms are to be considered as reference material for helping physicians in selecting the most adequate pathway according to the hospital facilities available.

The decisional algorithms are organized and diversified into three main situations (Figs. 1, 2, and 3) that suggest the same number of different practical behaviors aiming at guaranteeing the best care, albeit in different organizational situations. This really brings to the fore: the concept of network and of organization through the hub-and-spoke model.

Legend for the Algorithms

BP	blood pressure
HR	heart rate
GCS	Glasgow Coma Scale
EKG	electrocardiogram
CT	computed tomography
ICH	intracerebral hemorrhage
SAH	subarachnoid hemorrhage

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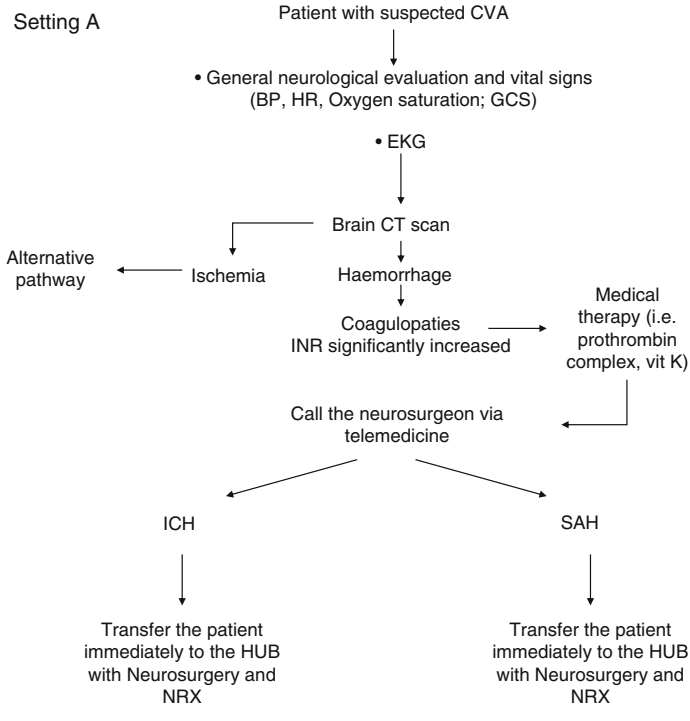
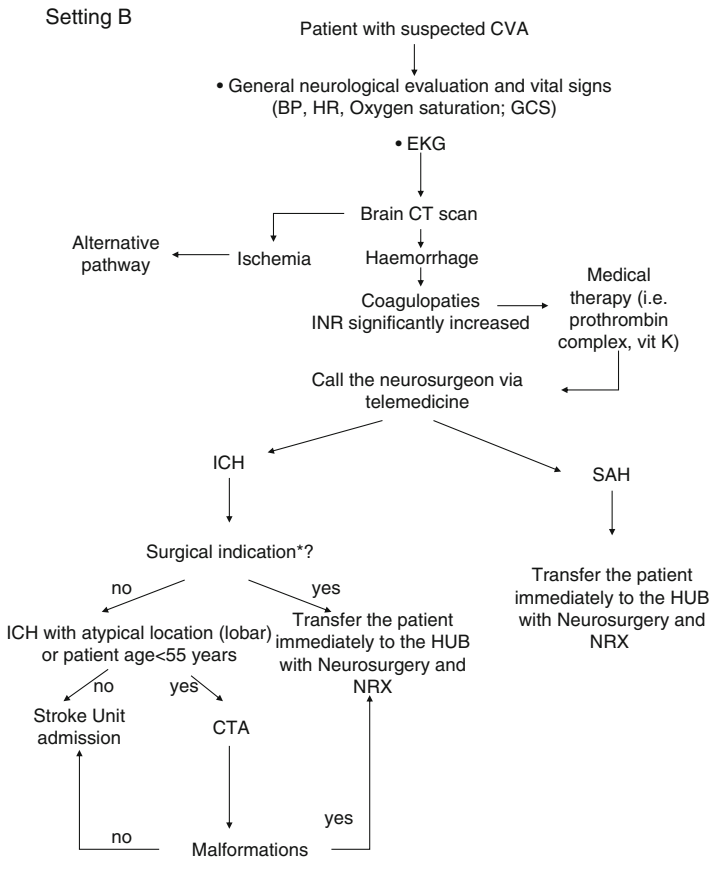
CTA	CT angiography
DSA	digital subtraction angiography
DC	decompressive craniectomy
ICP	intracranial pressure
NRX	neuroradiology
OR	operatory room
CVA	cerebrovascular attack

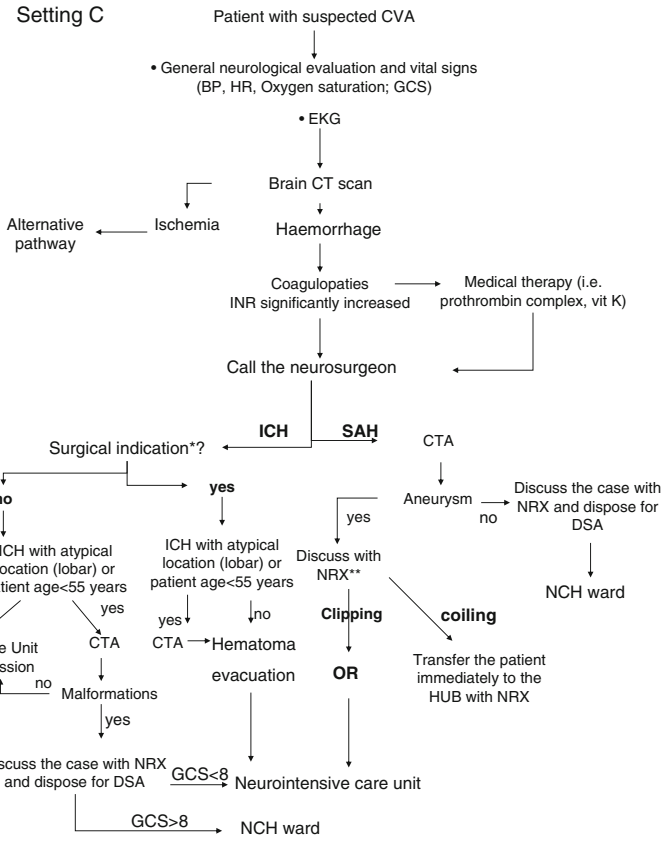
Table 4.1 Decisional algorithm

Setting A	
Hospital with:	Emergency department
	24/7 radiology service
	24/7 laboratory service
Setting B	
Hospital with:	Emergency department
	24/7 radiology services
	24/7 laboratory services
	24/7 neurology/stroke unit + hospital neurologist available
Setting C	
Hospital with:	Emergency department
	24/7 radiology services
	24/7 laboratory services
	24/7 neurology/stroke unit
	Neurosurgery
Setting D	
Hospital with:	Emergency department
	24/7 radiology services
	24/7 laboratory services
	24/7 neurology/stroke unit
	Neurosurgery
	Neuroradiology/interventional neuroradiology


Setting A
Patient with suspected CVA
• General neurological evaluation and vital signs (BP, HR, Oxygen saturation; GCS)
• EKG
Brain CT scan
Alternative pathway
Ischemia
Haemorrhage
Coagulopaties INR significantly increased
Medical therapy (i.e. prothrombin complex, vit K)
Call the neurosurgeon via telemedicine
ICH
SAH
Transfer the patient immediately to the HUB with Neurosurgery and NRX
Transfer the patient immediately to the HUB with Neurosurgery and NRX

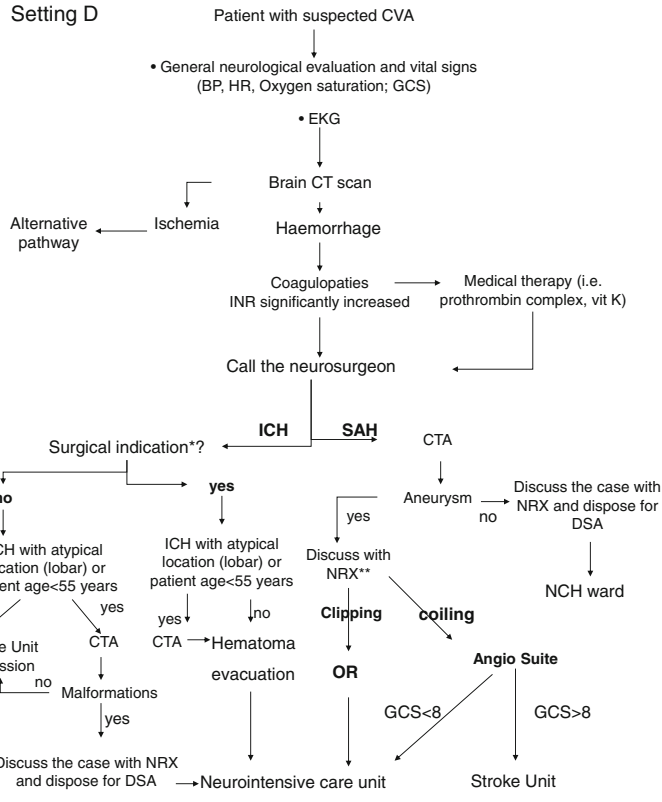


*Cerebellar hemorrhage with neurological deterioration or brainstem compression and/or hydrocephalus or supratentorial ICH with clinical deterioration or midline shift or clinical signs of elevated intracranial pressure



*Cerebellar hemorrhage with neurological deterioration or brainstem compression and/or hydrocephalus or supratentorial ICH with clinical deterioration or midline shift or clinical signs of elevated intracranial pressure

** In favour to clipping: young age, good clinical conditions, ACM aneurysm, associated intracerebral hematoma



*Cerebellar hemorrhage with neurological deterioration or brainstem compression and/or hydrocephalus or supratentorial ICH with clinical deterioration or midline shift or clinical signs of elevated intracranial pressure

** In favour to clipping: young age, good clinical conditions, ACM aneurysm, associated intracerebral hematoma